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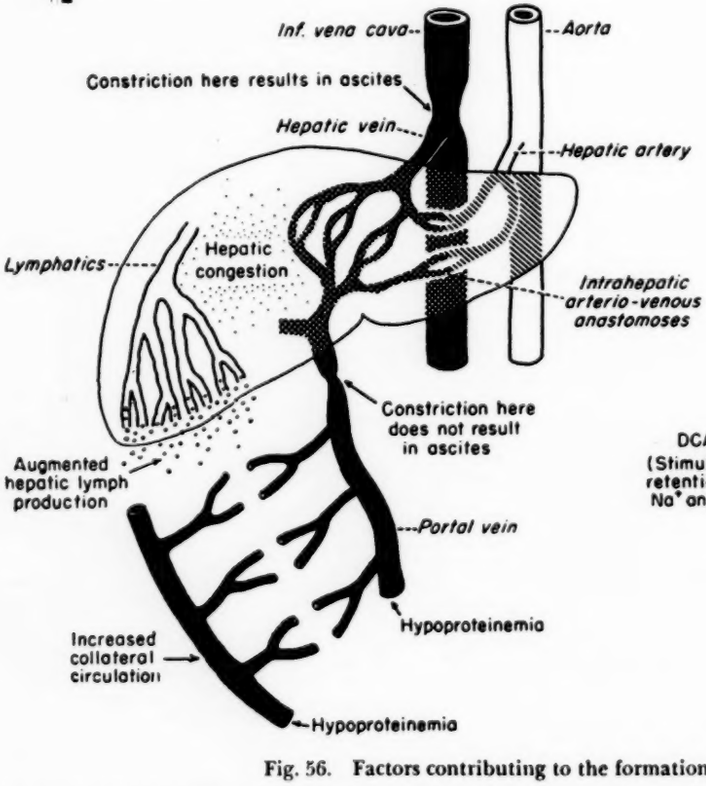

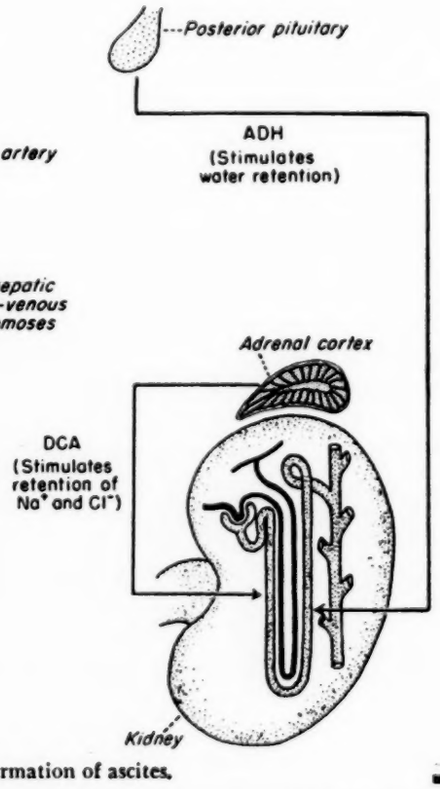

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Fig. 56. Factors contributing to the formation of ascites.

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ROLE OF THE GENERAL PRACTITIONER IN CANCER DETECTION

Russell S. Boles, M.D., Philadelphia, Raymond F. Kaiser, M.D.
and
William S. Baum, M.D., Bethesda, Md.

• Cancer must be expected to increase in importance as a medical problem, not only because of the changing character of the population but also because silent and subclinical forms of cancer are being recognized and the underreporting of cancer in the past is being corrected.

The 225,000 deaths per year now ascribed to cancer in the United States are offset by an estimated 23,000 cures. Early diagnosis and prompt, effective treatment by all known accepted methods constitute our only means of combating this disease. The hope for more diagnoses in the early stages rests especially on the fact that cancer in about half the cases begins at sites accessible to direct examination; examples are the female breast (21.7% of all cancer in women) and the skin (15.4% of all cancer in men).

The alert and thorough physician is still the indispensable factor in cancer control, but his responsibility extends beyond prevention and cure. The care of apparently incurable patients is also a responsibility of the profession. The thousands of patients in whom wide metastases make cure apparently hopeless need palliative and supportive therapy. Meanwhile, fatalism and fear must be dissipated by a more aggressive and confident attack on this devastating disease.

Fatalism and fear are cancer's allies. Despite the vast sums spent on cancer education, which clearly suggests that cancer can be cured, a large number of laymen and physicians maintain a fatalistic and defeatist attitude toward the disease. There are others who do not like to face unhappy situations and for this reasons refuse even to think about it. Finally, there are those who exhibit sheer indifference. Such attitudes, of course, permit a continuing toll of death and disability that need not occur. Obviously, in the battle against cancer, most of these individuals are not impressed by the progress being made. Perhaps many feel the same way about annihilation by an atomic bomb and remain indifferent to civilian defense measures set up for their protection. Undoubtedly others hear too much about cancer, so that it ceases to excite their curiosity or concern; they will not come to life until something dramatic happens in the field of cancer study. Whatever their reasons may be, the indifference of these individuals serves to hinder progress in cancer detection and control for themselves as well as others.

It must be granted that progress in the control of cancer has been slow, laborious, and without color; the story of cancer is not a happy one; originally it was grim and fraught with terror. Until recent years, reference to cancer was taboo, and the use of the word itself was vulgar—it connoted shame and stigma. This has not been entirely erased from the public mind, and until it is there will be those who choose to seek darkness rather than light in the field of cancer. At the moment, important and well-informed groups believe the best answer to the problem is continued education. However, in view of the magnitude of the problem, it would seem desirable to reevaluate educational programs to the end that more effective cooperation will be secured from the public and that a greater sense of opportunity as well as responsibility will be stimulated within the profession. We will consider the latter aspects of the subject of educational programs.

General Practitioner's Influence

Among the agencies assuming a leading role in cancer education of the medical profession is the National Cancer Institute of the United States Public Health Service. This institute assigns practically all of its funds for cancer education to the following purposes: undergraduate teaching grants to all of the medical schools in the country; clinical traineeships to support physicians for advanced education in cancer; support of cancer projects for applied research and the development of cancer control activities; and production of teaching films on cancer diagnosis for professional audiences. It

From the University of Pennsylvania School of Medicine and the Cancer Control Committee (Dr. Boles) and the Field Investigations and Demonstrations Branch (Drs. Kaiser and Baum), National Cancer Institute, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

Read before the General Scientific Meetings at the 104th Annual Meeting of the American Medical Association, Atlantic City, June 6, 1955.
Benjamin Carroll, Biometry Section, National Cancer Institute, gave statistical advice and prepared the tables.

stands to reason that the best results from the amount of money expended, in terms of benefit to the public, are dependent in no small measure on the cooperation of the general practitioner. It is to his efforts we must look for further progress, since he wields an extraordinary influence in the control of this disease. His influence holds sway in his office and on his daily rounds, during which time he can begin by developing among his patients a more wholesome attitude on the subject of cancer by encouraging them to bring it out in the open and not look upon it as a terrible killer that ravages at will a large, unalterable number of victims. After all, we should know by now that cancer can spend its fury only when it is concealed by the patient or overlooked by the physician.

That cancer is a medical problem of the first magnitude may be surmised from the fact that it accounts for approximately 225,000 deaths annually in the United States. It is estimated, furthermore, that within the next 20 years the recorded deaths from cancer will total 326,000 per year.[1] Devastating as these figures are, it is believed by some that the situation is even more serious than they indicate. Steiner [2] estimates, for instance, that underreporting of cancer, due to such factors as omission on death certificates and failure of diagnosis, accounts for a number equal to about 20% of all reported cancer deaths. In addition to this, it has been estimated from the present survival rates that about 23,000 cancer patients are cured annually.[2] It is known also that many types of cancer are silent or subclinical; these are sometimes found at autopsy, which has usually been performed for reasons other than the possibility of cancer. It has been estimated that 14,500 such cases occur annually.[2] This all indicates that, in addition to the 225,000 deaths previously quoted, there is an additional potential of approximately 79,000 cases that must be considered in assessing the gravity of the cancer problem.

Early diagnosis and prompt effective treatment by all known accepted procedures constitute our only means of combating this disease. To secure earlier diagnosis, coordinated efforts are being made throughout the country to develop cancer diagnostic tests; it can only be hoped that the continued intensive research being conducted will soon bear results. While cancer may not be due to an infection, we nevertheless are in a position analogous to that of the pre-Wassermann period, when the ravages of syphilis went unrecognized and untreated until irreparable damage was done. The success of any cancer control program will depend in large measure, as previously stated, upon the cooperation and vigilance of the general practitioner. The promptness with which he arrives at a diagnosis and utilizes appropriate therapeutic services is frequently the major factor in the survival of the patient.

The probability of the physician's detecting cancer in his own office is greater than he thinks. It is a strange paradox, however, that, while cancer invades nearly every organ of the body, it frequently escapes detection because the physician lacks suspicion of it. If cancer is to be found, the physician during every examination must think in terms of cancer. There is no greater incentive for searching for cancer in every patient than to find it in one. Be it a nodule in the thyroid, a lump in the breast, a mass in the rectum, or a supraclavicular node, its discovery and the prompt confirmation that it is malignant will stir one as nothing else can. Rewarding as all of this is to patient and doctor, it must be appreciated by those who promote programs in which they have never participated that the busy general practitioner with a multitude of things on his mind is not going to find it easy to devote a great deal of his office time to looking for signs of cancer. To be realistic about this matter, we must realize that many physicians simply do not have the time or equipment to render the services required in looking specifically for cancer. In fairness to such physicians, the plea is made that they think in terms of cancer when examining their patients and that they try to uncover any symptoms that may betray its presence. It is then recommended that the patient be referred for any studies that are indicated but that the physician is unable to conduct. However, as many of us who have been in general practice know, procedures for detection can be simplified, and a rewarding diagnosis is not so much a matter of time as it is of focusing attention on those body sites that are readily accessible to examination for cancer.

One-Half of All Cancer in Accessible Sites

If one lacks incentive for conducting routine examinations for cancer detection in his office, let him consider the results of the morbidity surveys conducted in 1937 and again in 1947 by the National Cancer Institute in 10 large metropolitan areas within the United States. The population represented by these areas comprised over 14 million people. Data from these surveys indicate that one-half of all cancer involves sites that are accessible to direct examination, in other words, sites that can be routinely examined in the physician's office.[3] The data provide the startling information that fully 50% of our cancer problem can be met by the use of practical office procedures. In most cases, these procedures, which require little or no special equipment, are nothing more than a patient expects as part of any complete and adequate physical examination. Furthermore, if cancer is to be discovered early, such examinations should be periodically conducted and promptly repeated with the development of symptoms suggestive of cancer. Frequent references to the need for periodic or repeated examinations of any sort are not made without our being conscious of the fact that many patients will not submit to such repeated examinations and, in fact, fail to see the need for them, which, of course, puts the physician on the defensive and at times in an embarrassing position.

1. Cutler, S. J., and Haenszel, W. M.: The Magnitude of the Cancer Problem, Pub. Health Rep. **69**: 333-339 (April) 1954.

2. Steiner, P. E.: An Evaluation of the Cancer Problem, Cancer Res. **12**: 455-464 (July) 1952.

3. Cutler, S. J.: Cancer Illness Among Residents of Atlanta, Ga.; Grodowitz, W.: Cancer Illness Among Residents of San Francisco and Alameda Counties, Calif.; Warren, I. I.: Cancer Illness Among Residents of New Orleans, La.; Marcus, S. C.: Cancer Illness Among Residents of Denver, Colo.; Cutler, S. J.: Cancer Illness Among Residents of Pittsburgh, Pa., Cancer Illness Among Residents of Chicago, Ill.; Marcus, S. C.: Cancer Illness Among Residents of Dallas, Texas, Cancer Illness Among Residents of Birmingham, Ala.; Cutler, S. C., and Rowen, J. C.: Cancer Illness Among Residents of Detroit, Mich.; Cutler, S. J., and Marcus, S. C.: Cancer Illness Among Residents of Philadelphia, Pa.; Cancer Morbidity Series 1-10, Federal Security Agency, United States Public Health Service, National Cancer Institute of the National Institutes of Health, 1950-1952.

Among the accessible sites to which we have reference, we might first consider the female breast. In table 1, it will be observed that breast cancer represents 21.7% of all cancer in females. It can be discovered simply enough by means of a thorough examination of the breasts; in this site alone represents one-fifth of the total accessible

TABLE 1.—*Percentage of Cancer Involving Sites Accessible to Direct Examination* *

	% of All Cancer in	
	Males	Females
Buccal cavity and pharynx	6.3	2.0
Thyroid	0.3	1.1
Breast	0.6	21.7
Skin	15.4	10.7
Prostate	9.5	0.0
Uterus	0.0	18.9
Rectum	6.5	4.5
Total	38.0	58.9

* Source: Cutler and Haenszel.[3]

cancer in both sexes. In cancer in this site, the physician is frequently aided by the patient, as 90 to 95% of breast cancer is first discovered by the woman herself, usually accidentally.[4] The physician who is interested in early diagnosis can secure considerable assistance in the discovery of breast tumors by teaching his patients a satisfactory technique of self-examination of the breasts. The importance of such examinations is attested by the fact that one out of three breast tumors usually is cancer.

In uterine cancer, which represents 18.9% of all cancer in the female, a technique is available for discovery of this lesion, part of which any physician can carry out in his office simply and inexpensively. This is the cytological technique developed by Papanicolaou and Traut, which can reveal the existence of cervical cancer even in the absence of significant signs or symptoms and without suggestive gross findings. The specimen secured by the physician must, of course, be submitted to one especially trained in its preparation and interpretation. Thus, the physician, by obtaining a routine vaginal smear on his patients and performing a pelvic examination including the use of the speculum, can contribute much to the early discovery of cancer in this site. Many physicians in general practice will not agree that this is a practical suggestion, but recent studies indicate the vaginal smear technique to be an efficient case-finding method for detecting early cancer.[5]

The mouth and pharynx are other parts of the body easily accessible to inspection and palpation. Of all cancer, 6.3% in males and 2.0% in females occurs in these sites. It takes but a moment or two to examine the lips, tongue, buccal mucous membrane, gums, tonsils, and pharynx and then to examine the neck and supraclavicular fossae for enlarged glands. Similarly, the thyroid should be carefully examined. Careful inspection of the skin of the entire body holds great potential for discovering cancer, since 15.4% of all cancer in males and 10.7% in females occurs in this site. Thorough examination and referral for biopsy could result in detection of a sizable number of cancers of this type, which are among the most curable. In males the prostate accounts for 9.5% of all cancer and the rectum for 6.5%. As 50% of cancer of the rectum and colon occurs within reach of the examining finger, the possibilities from a routine digital examination of the rectum, preferably with the patient in a squatting position, may well be imagined.[6]

Despite the fact that the types of cancer discussed so far are accessible to direct examination and, therefore, should be discovered at an early stage, many are not diagnosed until metastases have occurred. As demonstrated in table 2, it will be observed in the data from the previously mentioned morbidity survey of 10 cities, based on a population of over 14 million, that 59% of breast cancer and 55% of rectal cancer is not diagnosed until metastases have occurred. Similarly, 50% of prostate cancer and 43% of cancer of the uterus is not diagnosed until invasion has taken place. Perusal of the one-year survival rates alone for this group shows how much remains to be accomplished.

Cancer in Inaccessible Sites

Cancer in sites other than those accessible to direct examination presents a problem in early diagnosis that is more complex but whose solution can be, as in the case of the former, rewarding. The digestive system accounts for 27.8% of all cancer, the stomach and the colon being the organs more frequently affected. The over-all five-year survival rate for gastric cancer is not

TABLE 2.—*Cancer Diagnosis and Stage of Disease* *

	All Cancer, %	Diagnosed After Metastases, %	Survived One Year, % †
Sites Accessible to Direct Examination			
Buccal cavity and pharynx	4.0	36	76
Thyroid	0.7	38	79
Breast	11.6	59	82
Skin	12.9	6	96
Prostate	4.5	50	65
Uterus	10.0	43	78
Rectum	5.4	55	61
Sites Not Accessible to Direct Examination			
Digestive system	27.85	68.4	42
Stomach	7.79	78.8	32
Large intestine	7.73	63.7	53
Respiratory system	7.12	60.5	38
Lung and bronchus	5.49	74.3	29
Urinary organs	5.08	39.9	63
Leukemia	2.23	00.0	35
Lymphoma	2.85	82.4	66
Brain and central nervous system	1.87	20.0	46

* Source: Cutler and others.[3]
† Includes all stages at diagnosis.

appreciably better than 5%, while that for neoplasms of the colon is approximately 21% [7]; however, it has been reported that, in those patients with gastric cancer on whom operation is performed while the lesion is still

4. Kaiser, R. F.: Forward Glances in Cancer Control, GP **7**: 47-50 (March) 1953.

5. Erickson, C. C.: Exfoliative Cytology in Mass Screening for Uterine Cancer, Memphis and Shelby County, Tennessee, CA **5**: 63-64 (March) 1955.

6. Ackerman, L. V., and del Regato, J. A.: Cancer: Diagnosis, Treatment and Prognosis, ed. 2, St. Louis, C. V. Mosby Company, 1954, p. 615.

7. Ottenheimer, E. J., and Oughterson, A. W.: Observations on Cancer of the Colon and Rectum in Connecticut: Analysis Based on 5572 Proved Cases, New England J. Med. **252**: 565 (April) 1955.

localized, up to 50% five-year survivals have resulted.[8] It must be conceded that such results are unique and have not been duplicated in general surgical experience; however, the figure does serve to emphasize the promise of early diagnosis and treatment of these lesions. Early diagnosis of cancer of the digestive tract will require special studies in those over 45 years of age who complain of any persistent or recurrent gastrointestinal symptoms or intestinal disturbances, however mild they may be. In the office, such simple tests as a benzidine or guaiac test for occult blood on the specimen obtained during the rectal examination may be made. In most cases, these individuals will have to be referred for an x-ray examination and for a gastric analysis either of the conventional type or a tubeless analysis according to the technique of Segal. Cytological examinations of specimens obtained from the esophagus, stomach, colon, and rectum may also yield useful diagnostic information. Patients known to harbor such potentially precancerous conditions as polyps, atrophic gastritis, pernicious anemia, and achlorhydria should be periodically checked. Lesions such as polyps and gastric ulcer that exhibit the slightest sign of malignancy should be surgically removed whenever possible.

TABLE 3.—*Five-Year Cancer Survival* *

Relatively Accessible Primary Site	Cases, No.	Total Lost to Follow-Up	Surviving, % †		Ratio, Observed and Expected
			Observed	Expected	
Buccal cavity and pharynx	2,529	235	38.1	79.4	48.0
Breast, female	7,059	555	44.8	86.7	51.7
Genital organs, male	3,060	199	22.8	68.8	33.1
Genital organs, female	6,983	579	39.4	89.1	44.2
Skin	5,208	830	66.9	77.3	86.5
Relatively Inaccessible Primary Site					
Digestive system and peritoneum	15,925	468	12.0	79.6	15.1
Respiratory system	2,900	47	9.4	83.6	11.2
Urinary system	2,566	157	24.0	78.8	30.5
Soft tissue	397	38	46.6	88.3	52.8
Brain and central nervous system	805	38	19.9	91.3	21.8
Leukemia	1,382	30	6.2	86.4	7.2

* Source: Pollack.[9]

† Adjusted for age distribution of cancer patients.

The respiratory system accounts for over 7% of all cancer. When one takes into account the preponderance of this disease in males, it becomes apparent that particular attention should be paid to the detection of lung cancer in all men, especially in those over 40 years of age. Concentrated study in this group may cause a material upward adjustment of the present disappointing survival rates. Again, in addition to the general examination, x-ray of the chest at frequent intervals remains the only generally available diagnostic aid. Cytological study of repeated sputum specimens offers real promise as a future screening aid in the detection of early cancer of the lung.

As compared to cancer in accessible sites, diagnosis related to the stage of disease in cancer in sites not accessible to direct examination is far from encouraging, as is shown in table 2. Over 78% of stomach cancer and over 74% of lung cancer is not diagnosed until after metastases have occurred; this is also true of over 63% of cancer of the large intestine and over 39% of cancer of the urinary organs. While one-year survival rates in accessible cancer are discouraging, the comparative survival rates in this nonaccessible group are even more so —32% of patients with stomach cancer and 29% with lung cancer were found to survive one year; other one-year survival rates are comparably low, indicating again the need for early diagnosis.

Five-Year Survival Rates

It is recognized that one-year survival rates are of limited value. For this reason, data on the five-year survival rates of cancer in major sites, obtained from the Connecticut State Department of Health, are presented.[9] The observed percentage of survival in each group is based on mortality from all causes; the expected survival was obtained by the actuarial method, as recorded by Pollack.[9] The ratio of observed to expected survival percentages should reflect the impact of cancer on survival, exclusive of other causes (table 3).

Pollack's study reveals that, among the accessible sites, the computed five-year survival for cancer of the breast in the female is 51.7% of the rate that would be expected in a representative population of the same age composition, regardless of the presence of cancer. The corresponding figure for buccal cavity and pharynx is 48.0%, for male genital organs, 33.1%, and for female genital organs, 44.2%. While these figures relating to disease in relatively accessible sites may appear discouraging, those relating to cancer in inaccessible sites are a cause for actual alarm. The latter figures, as shown in table 3, demonstrate the computed five-year survival rate for patients with cancer of the digestive system and peritoneum to be 15.1%, and only 11.2% of patients with cancer of the respiratory system survive for a similar period.[9] Data of this type on survival in general population groups are most valuable in bringing into focus the tremendous potential for improvement that exists in the field of cancer. The majority of survival data to date is based upon selected hospital population groups. It is evident that the continuation of such an important study as the one now being conducted by the Connecticut State Department of Health, referred to above, will furnish data of great value in evaluating diagnostic and therapeutic trends in cancer.

While the patient is frequently at fault in delay in diagnosis of cancer, we must admit that the physicians themselves must accept their share of responsibility for the depressing picture these figures portray. By physicians we are by no means alluding to the general practitioner alone—no more than to other groups. In conformance to present methods of medical education and

8. Wangensteen, O. H.: Cancer of the Esophagus and the Stomach: Monograph for Physician, Early Recognition of Cancer Series, no. 6, New York, American Cancer Society, 1951, p. 98.

9. Pollack, E. S.: The Effect of Age and Site on Life Expectancy of Cancer Patients, Connecticut Health Bull. 68, 1954.

certification, many young physicians are influenced prematurely to specialize long before they are fundamentally prepared for it.

Need for Early Diagnosis

Throughout this discussion, much stress has been placed upon early diagnosis and prompt effective treatment. That this approach is satisfactory and that the picture can be brightened is illustrated in table 4, which presents data again taken from the reports compiled by the Connecticut State Department of Health.[10] This interesting data shows the improvement in five-year survival as related to stage of disease. It is highly impressive data, as it reveals what can be accomplished in saving lives. In 1935 it is noted that in localized cancer, the five-year survival rate was 31%, as compared to 18% for regional involvement and only 1.6% for those patients with remote metastases. From 1935 to 1943, a period of eight years, a heartening improvement in the survival rates of patients with localized cancer occurred, i. e., from 31 to 42%. No such improvement is noted in those with regional involvement or in those with remote metastases. Again we observe that early diagnosis is

TABLE 4.—*Improvement in Five-Year Survival by Stage of Disease, 1935 to 1943* *

Year Diagnosed	Patients, No.			Survived, % †		
	Localized	Regional Involvement	Remote Metastasis	Localized	Regional Involvement	Remote Metastasis
1935	1,013	372	327	31	18	1.6
1937	1,042	476	424	38	16	1.2
1939	1,310	595	474	42	19	1.5
1941	1,516	664	448	43	22	1.4
1943	1,558	753	485	42	19	2.9

* Source: Pollack.[10]

† Based on mortality from all causes.

our immediate and most effective weapon in dealing with cancer. Research and prevention offer promising future potential aid, but immediate improvement rests almost entirely with the physicians themselves who are entrusted with this great responsibility.

With all due respect to newly developing techniques, it must still be recognized that the indispensable factor in cancer control is the alert and thorough physician. It appears that the application of known simple techniques plus care and diligence can materially improve the disappointing statistical summary that our tables portray. To offset this, however, we have the knowledge that 50% of the total cancer problem is subject to control by means of direct examination of accessible sites. These figures illustrate, furthermore, how 50% of cancer that is less accessible can be materially reduced by the application of careful examination and simple accessory aids and the employment of such special examinations as may be required.

Care of Incurable Patients

The major emphasis in this paper has been upon early diagnosis, prompt treatment, and consequent improved recovery rates. The physician's responsibility does not stop there, however. It is his duty not only to cure disease but to relieve suffering. This leads directly to what we consider a most important message in this paper. Our tables have strikingly shown that many thousands of patients suffer from cancer that has metastasized widely and for whom there is no apparent hope of cure—they constitute the majority of those afflicted with cancer. Their survival rates after any kind of treatment are acknowledgedly a cause for dismay. Despite this, they remain the responsibility of the physician—they must receive palliative and supportive therapy and should not be cruelly consigned to a lingering fate assuaged to some degree by sedatives and narcotics. Even surgery that holds no promise of cure may still be due them, and radioisotope therapy that by chance may provide some measure of relief must not be denied them.

Too often patients with advanced cancer are told that their condition is hopeless, that nothing more can be done for them. If such information is not actually communicated to the patient, an impression of it is created by an air of futility and a lack of any suggestion for the relief of their physical and mental anguish. Many patients so treated will seek help from other quarters where they will find comfort and understanding, albeit they do not receive the benefits of our present knowledge and accepted modern techniques. This is unfortunate for the patient but much more so for the medical profession, as every patient forced to such recourse reflects discredit on the profession. The care of these apparently incurable patients is the responsibility of the profession. It provides a unique opportunity to practice the art of medicine, and for this reason it should be jealously guarded by the physician.

Fatalism and fear are indeed cancer's allies. While some may say the very figures presented in this paper justify such attitudes, let them remember there is also evidence to show that these attitudes can and will be dissipated by a more aggressive and confident attack on this devastating disease.

Rittenhouse-Plaza (3) (Dr. Boles).

10. Pollack, E. S.: Cancer Survival Picture Brightens, Connecticut Health Bull. 67, 1953.

Treatment of Tuberculosis.—The problem of treatment of pulmonary tuberculosis is made difficult and complicated because of the advanced stage of the disease in most cases. Chemotherapy has more certain and sustained effects on tuberculosis than rest treatment alone. Resolution and fibrosis are more rapid and complete, but the healing processes are substantially the same as those observed in the natural course. Necrosis of tissue may be averted or retarded. Chemotherapy is indicated in all cases of manifestly active tuberculosis, and patients should have the added benefit of rest treatment, at least until the disease is controlled. Most patients profit by undergoing institutional treatment at the start, and many for long periods of time. Under suitable conditions, some may complete treatment satisfactorily at home. Regimens of chemotherapy, once started, usually should be continued for a year or longer without interruption and with only minor modifications. With few exceptions, two drugs are administered simultaneously in order to delay bacterial drug resistance. In present-day treatment, the possibilities of success depend more than ever before on early diagnosis, the proper evaluation of the individual case, and the planning and execution of long term management. In far advanced cases life may be prolonged, but the eventual relapse and mortality rates are high. In less advanced and minimal cases the prospects of permanent recovery are excellent; in some, this is best assured by the aid of surgery.—J. Burns Amberson, M.D., Evaluation of the Present-Day Treatment of Pulmonary Tuberculosis, *Annals of Internal Medicine*, December, 1955.

OBSERVATIONS ON CLINICAL USE OF PHENOXYMETHYL PENICILLIN (PENICILLIN V)

William J. Martin, M.D., Donald R. Nichols, M.D.
and
Fordyce R. Heilman, M.D., Rochester, Minn.

• *Penicillin V resists gastric digestion and is effective when given by mouth. Satisfactory concentrations in the serum were found during treatment with 200,000 units given every four hours and were adequate for minor infections with susceptible organisms. In the most severe infections, such as bacterial endocarditis, the dosage can be raised to one million units.*

The action of penicillin V was studied in 18 patients. Four illustrative case histories are given in some detail. The most frequent untoward reaction was gastrointestinal, and one patient had a rather severe aphthous stomatitis, but the more severe allergic reactions were not encountered.

Phenoxymethyl penicillin (penicillin V) [1] represents an advance in therapy with penicillin because it has been found to be effective when administered by the oral route. It is produced biosynthetically by Penicillium chrysogenum Q 176 in a culture medium that contains a special type of nutrient substrate. It is stable as a free acid and, unlike other penicillins, does not require preparation as a metallic or organic salt. It is chemically different from penicillin G and exhibits a high degree of stability in the presence of gastric acids. Not being destroyed by acid in the stomach, as is penicillin G, penicillin V remains available in larger amounts for absorption. The fact that penicillin G is destroyed by the gastric acids has been advanced as one of the reasons that it is inadequate for oral use in serious infections. On the other hand, penicillin V, undisturbed by the acid gastric juice and soluble in the alkaline medium of the small intestine, is fully available for absorption, and serum concentrations of this penicillin should be more dependable and predictable.

Bacterial Sensitivity and Resistance

In our laboratories, comparative tests of the sensitivity of Micrococcus pyogenes to penicillin V and penicillin G have shown that penicillin V is usually more active than penicillin G on a unit-for-unit basis [1a]; some strains of this organism are almost twice as sensitive to penicillin V as to penicillin G, but others are about equally sensitive to the two agents. The results of sensitivity tests of organisms other than M. pyogenes to penicillin V suggest that this agent has an antibacterial effect similar to, if not duplicative of, that of penicillin G.[1a] It is evident that there is cross resistance between these two penicillins; strains resistant to one are resistant to the other.

Absorption

The data in table 1 indicate that, in patients who first receive a single dose of 200,000 units of penicillin V and later receive an equal amount of penicillin G, (1) the median levels of penicillin V in the serum are higher than are the median levels of penicillin G, and (2) often some penicillin V is present in the serum through the sixth hour after administration, whereas penicillin G has nearly always disappeared from the serum before the sixth hour. These data are in agreement with those of other investigators.[2]

The data in table 2 indicate that in patients to whom 200,000 units of penicillin V is administered orally every eight hours the antibiotic does not "pile up" after successive doses at the interval given. These data also indicate that, in patients who receive an initial dose of 400,000 units of penicillin V and subsequent doses of 200,000 units every four hours, the median serum concentration of the antibiotic two hours after the administration of the initial dose is, as is to be expected, higher than the median serum concentration that is observed after the smaller initial doses of 200,000 units given to patients in the preceding category. Again there seems to be no tendency for the antibiotic to "pile up" in the serum after multiple dose, as evidenced by the fact that 50 hours after the initial dose had been given the median serum concentration was not higher than that noted in the same group of patients 2 hours after the initial dose. Finally the data in table 2 indicate that in patients who receive 400,000 units of penicillin V every 4 hours the agent does not "pile up" significantly even beyond 50 hours after the initial dose. The association of a higher median concentration in the serum with higher dosage

TABLE 1.—*Concentration in Serum After Administration of 200,000 Units of Penicillin V Followed Twenty-Four Hours Later by 200,000 Units of Penicillin G* *

Agent	Time After Single Oral Dose, Hr.	Units per Ml. of Serum		
		High	Low	Median
Penicillin V	2	1.32	0.175	0.53
	4	0.85	....	0.45
	6	0.25	....	0.16
Penicillin G	2	0.75	0.12	0.20
	4	0.37	....	0.07
	6	0.035	....	....

* In 11 patients.

From the Section of Medicine (Drs. Martin and Nichols) and the Section of Bacteriology (Dr. Heilman), the Mayo Clinic and Mayo Foundation.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

The phenoxymethyl penicillin used in this study was supplied by Wyeth Laboratories, Inc., Philadelphia.

1. (*a*) Martin, W. J.; Nichols, D. R., and Heilman, F. R.: Penicillin V, a New Type of Penicillin: Preliminary Clinical and Laboratory Observations, Proc. Staff Meet. Mayo Clin. **30**: 467-476 (Oct. 19) 1955. (*b*) Martin, W. J.; Nichols, D. R., and Heilman, F. R.: Penicillin V: Further Observations, ibid. **30**: 521-526 (Nov. 2) 1955.

2. Wright, W. W., and others: Serum Concentrations and Urinary Excretion Following Oral Administration of Penicillin V and Comparison with Penicillin G, Antibiotic Med. **1**: 490-495 (Sept.) 1955.

of the agent is evident on comparison. Further evidence of this association consists of the results obtained in 21 patients given 1 million units of penicillin V every four hours; in these patients the median serum concentration of the antibiotic two hours after the last dose was 3.52 units per milliliter, the range being from 1.2 to 15.45 units per milliliter. Simultaneous administration of penicillin V and probenecid (Benemid) produced higher concentrations of the antibiotic in the serums of five of seven patients two hours after administration than giving penicillin V alone.[1b]

Diffusion into Body Fluids and Tissues

In studies on the concentration of penicillin V in the cerebrospinal fluid and blood serum of nine patients without evidence of meningeal irritation who had received the agent, it was observed that in most instances the serum contained appreciable amounts of penicillin V but that in no instance did the cerebrospinal fluid contain detectable amounts.[1b] It should be pointed out, of course, that penicillin V, like penicillin G, may diffuse into the cerebrospinal fluid in the presence of inflammation. Additional studies [1b] indicated that penicillin V diffused readily into pleural fluid in one patient studied and into ascitic fluid in four patients studied. It was excreted in the bile in a biologically active form in five patients, and it was present in thyroid tissue in six patients when appreciable amounts were present in the serum.

Dosage and Clinical Trials

From the data derived from our studies on absorption of penicillin V we have, in general, adopted the policy of administering the agent orally at intervals not exceeding four hours. In relatively minor infections we have given the agent at intervals of six and eight hours. We have given it as often as every hour when the illness appeared to indicate the need for a higher, sustained concentration of the antibiotic in the serum and tissues. Treatment with 200,000 units of penicillin V given every four hours has been found effective in minor infections due to organisms susceptible to the action of the drug. For infections of moderate severity, the administration of 400,000 units every four hours appears adequate. We have given 800,000 units for fairly severe infections. As will become apparent, we have relied on the agent in amounts of 1 million units in combination with other agents for the most severe infections, such as bacterial endocarditis. Although we have given individual doses of 2 million units, we are currently investigating the plausibility of combating some of the severe infections with smaller doses.

The antibacterial activity of penicillin V, its lack of any apparent serious toxicity, and especially its absorption after oral administration prompted us to use it in the treatment of a number of infections. Some of our clinical experience with this agent is summarized in table 3. Brief reports of four cases follow.

Report of Cases

CASE 3.—A 56-year-old woman came to the Mayo Clinic in September, 1955, for a routine examination. In 1948, while she was being examined at the clinic, she described crops of furuncles that appeared on her extremities, usually in the late summer. She also stated that three of her children were victims of the same affliction. At the time of examination in 1948 a furuncle on the dorsum of the left hand was noted. M. pyogenes was cultured from the material exuding from the lesion. The patient was advised to take penicillin G by the oral route at the first appearance of a furuncle; later she said that this regimen was quite satisfactory in controlling her complaint. However, in 1949 and again in 1953 she was examined at the clinic because of cystitis, also due to M. pyogenes.

The day after admission to the clinic in September, 1955, the patient interrupted her schedule of laboratory tests and returned, because of complaints referable to her left elbow, to the internist who was supervising her examination. Over a period of 24 hours the elbow had become red, hot, painful, and swollen. It was exquisitely tender, and evidence of excess fluid in the joint was noted. Motion of the joint was very painful, and the skin overlying the joint was sharply elevated as in an erysipeloid reaction. The patient stated that the elbow felt as if she "had a boil, right in the joint." X-ray examination of the left elbow gave negative results, and the concentration of uric acid in the serum was within normal limits. Since the patient ostensibly had long been prey to infections with M. pyogenes, and since the complaint had all the earmarks of acute infectious arthritis, therapy with penicillin V in amounts of 400,000 units given every four hours was instituted and was continued for five days. Within 24 hours the inflammation began to subside, and after three days of treatment only local tenderness was elicited on physical examination.

TABLE 2.—*Concentration of Penicillin V in Serum After Various Dosages*

Dosage	Time After Initial Dose, Hr.	Units per Ml. of Serum		
		High	Low	Median
200,000 units every 8 hr. (9 patients)	2	1.83	0.57	1.02
	26	1.96	0.15	0.58
	50	4.2	0.85	0.62
400,000 units followed by 200,000 units every 4 hr. (10 patients)	2	2.69	0.195	1.38
	26	2.46	0.77	0.97
	50	2.19	0.35	1.14
400,000 units every 4 hr. (8 patients)	2	3.84	0.72	1.64
	26	4.4	0.55	1.74
	50	3.15	1.89	2.31
	74	3.72	0.21	2.37

CASE 4.—A 28-year-old man was admitted to the hospital because of multiple draining abscesses of the left axilla of two weeks' duration. One month previously a furuncle had developed on the left wrist; this had been incised and drained, and penicillin G had been administered intramuscularly. The lesion of the left wrist had healed rapidly, but, two weeks later, multiple, red, tender, warm, painful swellings began to appear in the left axilla, and some of these swellings began to break down and drain thick yellow pus. Cultures of the pus revealed M. pyogenes. The patient was given penicillin V in amounts of 800,000 units every four hours for six days. The inflammation subsided, and drainage ceased within the six days.

CASE 17.—A 43-year-old man was admitted to the hospital with a complaint of swelling of the legs. Eight months previously he had been in an automobile accident and had subsequently been hospitalized for three weeks because of pain in the back and sciatica on the left side. Six months previously he had noted swelling in his legs, for which his local physician had prescribed digitalis and a diuretic to be taken by mouth. Two months previously he had begun to have night sweats. One month previously he had noted the appearance of small red spots on the pretibial surfaces, and at the same time he began to be seized with periodic shaking chills. Two weeks previously he had suffered sudden severe pain in the left upper quadrant of the abdomen and in the left flank, but this had gradually subsided during the ensuing week. Since that time he had noted anorexia and vomiting.

Positive physical findings included multiple ecchymotic areas on the legs; marked edema of the legs; a moderately loud, high-pitched, blowing diastolic murmur heard best over the aortic area and to the left of the sternum; and a palpable spleen. Seven cultures of the blood revealed Streptococcus mitis, which was

inhibited in vitro by 0.05 mcg. of penicillin per milliliter. Penicillin V was given in amounts of 1 million units every four hours. While the patient was on this regimen, the Str. mitis isolated from his blood was exposed to various dilutions of his serum. The dilutions of his serum were made in pooled normal human serum, and the serum-streptococci mixtures were incubated in an atmosphere containing 5% of carbon dioxide to control the pH. There was a total killing effect on the organism by his serum in a dilution of 1 to 32.

Treatment with 0.5 gm. of probenecid given every six hours was then added to the therapeutic regimen. While the patient was on the combined regimen, the Str. mitis isolated from his blood was exposed again to various dilutions of his serum, but there was no increased bactericidal effect after the addition of probenecid, since the total killing effect on the organism by the serum did not occur in a dilution of the serum greater than 1 to 32. Next, treatment with a combination of equal parts of streptomycin and dihydrostreptomycin was added to the therapeutic regimen; this combination was given by intramuscular injection every 12 hours in amounts of 1 gm. Serum taken from the patient while he was on this regimen produced a total killing effect on the Str. mitis in a dilution of 1 to 64. On the third day of therapy with penicillin V the patient's temperature became normal and remained so (figure). On the same day the results of blood culture were read as negative; the results of all subsequent blood cultures were also read as negative. The patient was treated for two weeks and dismissed from the hospital.

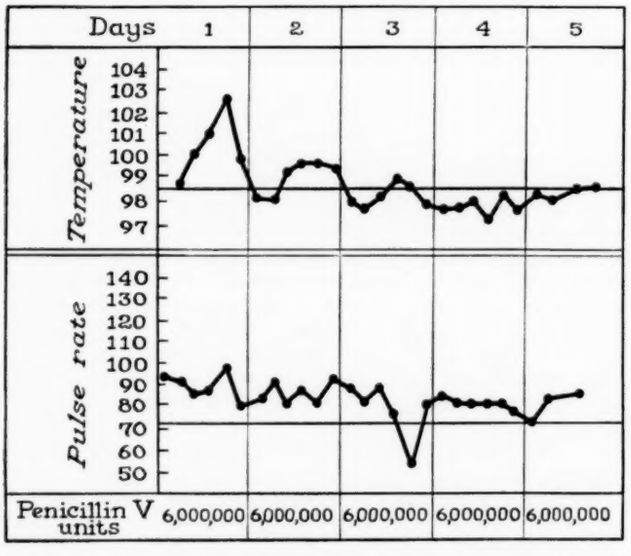
Case 18.—A 59-year-old man was admitted to the hospital because of a sinus on the plantar aspect of the right foot from which sanguinopurulent material was draining. He had had diabetes mellitus for three years, but the diabetes had ostensibly been controlled by manipulation of his diet. Three months previously an area overlying the proximal phalanx of the third toe of the right foot had become red, swollen, tender, and painful. This site had subsequently begun to drain, and the patient was hospitalized elsewhere. During the three weeks of hospitalization elsewhere he had received various antibiotic agents, apparently without effect on the disease process. He had been told he had osteomyelitis and amputation of the foot was indicated.

At the time of our initial examination an ulcer that was discharging sanguinopurulent material was present in the region described, the posterior tibial and dorsal pedal pulses were absent bilaterally, and roentgenograms of the right foot showed destructive changes consistent with those of osteomyelitis. Cultures of the material from the ulcer revealed M. pyogenes, which was inhibited by 1 unit of penicillin per milliliter. Initially, amputation of the foot was considered. He was given 400,000 units of penicillin V every four hours; after a week of such therapy the ulcer had healed. Therapy was continued for another 10 days.

Table 3.—*Clinical Trials of Penicillin V*

Case, No.	Clinical Diagnosis	Organism, Source and Name	Penicillin V: Dose, Units Every 4 Hr.	Penicillin V: Total Doses, No.	Results
1	Abscess, peritonsillar	Abscess (Micrococcus and nonhemolytic Streptococcus)	400,000	30	Cleared up without incision
2	Amputation stump, infected (sarcoma)	Wound (M. pyogenes)	400,000	21	Drainage ceased; became afebrile
3	Arthritis, acute infectious, left elbow	Furuncles and urine (M. pyogenes)	400,000	30	Excellent
4	Furunculosis (left axilla)	Furuncles (M. pyogenes)	800,000	36	Multiple furuncles cleared up without incision
5	Otitis media, acute	Ear (Str. pyogenes)	800,000	22	Satisfactory
6	Pharyngitis, acute	Throat (M. pyogenes)	400,000	15	Satisfactory
7	Pharyngitis, acute	Throat (Str. pyogenes)	400,000	33	Satisfactory
8	Pharyngitis, acute	Throat (M. pyogenes and Str. pyogenes)	400,000	12	Pharyngeal exudate disappeared; diarrhea and aphthous stomatitis developed
9	Pneumonia	Sputum (Diplococcus pneumoniae)	200,000 *	17	Had been treated elsewhere with penicillin G given parenterally. Became afebrile third day after receiving penicillin V
10	Pneumonitis (bronchiectasis)	Sputum (D. pneumoniae)	400,000 † 200,000 ‡	24	Hemoptysis ceased; became afebrile; roentgenograms cleared
11	Pneumonitis (tracheotomy)	Tracheal aspirate (M. pyogenes)	400,000	14	Satisfactory; became afebrile; roentgenograms cleared
12	Pneumonitis (tracheotomy)	Tracheal aspirate (Str. pyogenes)	200,000 *	17	Satisfactory; became afebrile; roentgenograms cleared
13	Sinusitis, acute	Nose (Str. pyogenes)	400,000	24	Satisfactory
14	Tonsillitis, acute	Throat (Str. pyogenes)	400,000	15	Satisfactory
15	Tonsillitis, acute, with cervical adenopathy	Throat (M. pyogenes)	400,000	24	Satisfactory
16	Urinary infection (prostatic carcinoma)	Urine (Str. faecalis)	400,000 † 200,000 ‡	31	Excellent; cultures of urine became negative
17	Subacute bacterial endocarditis	Blood (Str. mitis)	1,000,000 §	84	Excellent bacteriological response; blood cultures became negative on third day; treated for 2 wk.
18	Osteomyelitis and draining sinus, right foot	Sinus (M. pyogenes)	400,000	102	Excellent response; sinus healed after 7 days of treatment

* Given every 8 hr. † Initial dose. ‡ Subsequent doses. § 2 gm. of streptoduocin (Distrycin) and 2 gm. of probenecid (Benemid) also given daily.



Results of treatment with penicillin V in case of subacute bacterial endocarditis in which Streptococcus mitis was isolated (case 17).

Toxicity

The most frequently encountered untoward reaction after the oral administration of penicillin V has been, to date, mild gastrointestinal irritation manifested by slight abdominal cramping and an increased number of stools

that tend to be liquid in character. However, this type of reaction has not been noted in more than 5% of our patients and has not necessitated withdrawal of the agent in any of our cases. One of our patients experienced rather severe aphthous stomatitis, apparently due to the agent. Penicillin V may be capable of inducing the more severe allergic reactions such as anaphylaxis, but we have not encountered such reactions to the present time.

Comment

We have indicated that penicillin V appears useful in the treatment of many infections due to penicillin-sensitive organisms such as streptococci, pneumococci, and micrococci. Since some strains of micrococci appear to be more sensitive to penicillin V than to penicillin G, they may be more effectively controlled with penicillin V. The agent may also prove a boon in the prophylaxis of streptococcic infections in individuals susceptible to rheumatic fever and glomerulonephritis and preoperatively in patients with valvular or congenital heart disease.

Because of the better and more consistent absorption of penicillin V from the intestinal tract, it would appear that this type of penicillin is preferable to penicillin G when oral administration is to be used. Unless the patient is kept under close medical supervision when the oral route is employed, reliance must be placed on the individual's ability and willingness to follow instructions. Such reliance sometimes is not justified, and in such a situation intramuscular administration would seem preferable. Furthermore, in serious infections such as bacteremia and endocarditis we would recommend at present the oral use of penicillin V only when the infection is due to an organism that is very sensitive to penicillin.

Summary

Phenoxymethyl penicillin (penicillin V) appears to be readily absorbed into the serum when given orally. The concentration of it in the serum is higher two hours after administration than is the concentration of penicillin G after comparable oral doses, and this higher concentration appears to be maintained longer. The serum concentration of penicillin V usually begins to decline four hours after administration of the drug, although detectable amounts are present for six hours in most instances. The rate of excretion of penicillin V is rather constant in the absence of any impairment of renal function, and there appears to be no "piling up" of the antibiotic in the serum. Simultaneous administration of penicillin V and probenecid (Benemid) may at times produce a higher concentration of the antibiotic in the serum than the administration of penicillin V alone. It appears also that penicillin V is diffused rather generally throughout most of the body fluids, although it cannot be detected in the cerebrospinal fluid in the presence of noninflamed meninges. Results of treatment of a number of infections with penicillin V have been satisfactory.

PHENOXYMETHYL PENICILLIN (PENICILLIN V) THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

Edward L. Quinn, M.D., James M. Colville, M.D., Frank Cox Jr., M.D.
and
Joseph Truant, Ph.D., Detroit

• Penicillin V was compared with penicillin G as to the concentrations attained in the blood when the two antibiotics were taken by mouth. In eight normal fasting subjects the average serum concentrations showed that penicillin G was absorbed faster and reached a higher concentration during the first half-hour, but thereafter penicillin V reached concentrations 1.7 to 2.8 times as high as those of penicillin G, and this difference was found consistently at the end of the first, second, third, and fourth hours. Penicillin V also gave higher blood concentrations than did penicillin G when given to four patients orally at four-hour intervals over a period of weeks.

Case histories of two patients with bacteremia caused by alpha-hemolytic streptococci illustrated the effectiveness of orally administered penicillin V in bringing about a sustained clinical remission. A third patient, whose bacteremia was caused by Neisseria sicca, obtained clinical and bacteriological remission from a course consisting of 2 million units of penicillin V orally every four hours with 0.5 gm. each of streptomycin and dihydrostreptomycin intramuscularly twice daily. In a fourth patient, bacteremia caused by a Micrococcus pyogenes was halted but temporarily, and at the time of relapse the organism was found exceptionally resistant to antibiotics.

The following points have been established in the chemotherapy of subacute bacterial endocarditis [1]: 1. Penicillin is usually much more effective than other antimicrobial and chemotherapeutic agents. 2. The effectiveness of penicillin can be correlated grossly with the in vitro sensitivity of the infecting organism to this agent.[1e] 3. Moderately large doses should be given. 4. The period of chemotherapy must be of some length. While these general principles have been accepted, sufficient data are not yet available to finally define the most effective doses and methods of administration of penicillin in the treatment of this disease.

The parenteral route of administration has been widely advocated, and a large clinical experience with this method of penicillin therapy has been accumulated. On the other hand, because of certain pharmacological con-

From the Division of Infectious Diseases (Drs. Quinn, Colville, and Cox) and Department of Laboratories (Dr. Truant), the Henry Ford Hospital.

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The phenoxymethyl penicillin used in this study was supplied by Dr. Edward F. Roberts of Wyeth Laboratories, Inc., Philadelphia.

1. (*a*) Finland, M.: Medical Progress: Treatment of Bacterial Endocarditis, New England J. Med. **250**: 419, 1954. (*b*) Beeson, P. B: Subacute Bacterial Endocarditis: Optimal Duration of Treatment, editorial, Am. J. Med. **19**: 1, 1955. (*c*) Bloomfield, A. L.: Relation of Strain Sensitivity to Curative Dose of Penicillin in Subacute Bacterial Endocarditis, Acta med. scandinav., supp. 196, pp. 505-515, 1947.

siderations, the oral administration of penicillin in the treatment of subacute bacterial endocarditis has received little attention.[1a] It has been demonstrated [2] that previously available forms of penicillin exhibited failure of maximal absorption from the small intestine, so that only about 20% of an orally ingested dose was absorbed. In addition, a marked variability in the degree of absorption was noted. From these data it would appear that oral administration of pencillin is too unreliable and would require excessive amounts to insure adequate therapy for serious infections. Furthermore, it has been suggested by Finland [1a] that massive doses of penicillin given orally might result in toxic gastrointestinal reactions similar to those seen after the administration of the broad-spectrum antibiotics.

A recently developed form of penicillin, phenoxymethyl penicillin, or penicillin V,[3] which differs from penicillin G by a single oxygen molecule, has been shown to have some significantly different physical properties.

TABLE 1.—*Comparison of Blood Penicillin Concentration in Eight Normal Subjects After Oral Administration of Two Million Units of Penicillin V and Penicillin G as a Single Dose*

	Time After Administration, Hr.									
	½		1		2		3		4	
Subject	V	G	V	G	V	G	V	G	V	G
1	5.16*	6.99	4.81	5.98	2.17	2.11	3.47	1.98	4.47	0.74
2	8.91	4.35	12.08	7.33	5.40	3.77	3.64	2.50	1.31	0.87
3	3.30	5.67	6.81	6.09	7.20	3.07	4.61	5.03	2.84	2.00
4	10.66	10.99	8.71	7.71	8.57	4.03	9.86	2.37	7.55	0.88
5	8.91	....†	7.94	9.70	12.12	6.08	12.41	3.86	5.39	2.04
6	2.82	7.51	11.32	7.99	5.41	5.14	5.82	4.93	2.53	2.25
7	6.06	5.04	12.19	7.52	4.09	2.65	3.98	1.12	1.23	0.78
8	2.02	7.20	8.55	5.09	7.63	3.82	6.36	1.54	3.15	0.42
Av.	5.98	6.82	9.05	7.20	6.57	3.83	6.27	2.67	3.56	1.25
Range	2.02 to 10.66	4.35 to 10.99	4.81 to 12.19	5.09 to 9.70	2.17 to 12.12	2.11 to 6.08	3.47 to 12.41	1.12 to 4.93	1.31 to 7.55	0.42 to 2.25

* Values expressed as units per milliliter of serum.
† Not done.

This compound is notable for its high stability at pH ranges below 3.0, its low solubility in an acid medium, and its easy conversion to a water-soluble alkali in a neutral or alkaline pH. Earlier reports by others [4] indicated that relatively small oral doses of penicillin V, in the range of 200,000 to 400,000 units, resulted in higher and more prolonged blood levels and greater total urinary excretion when compared with penicillin G given by the oral route. Since oral therapy has the advantages of ease and convenience of administration and minimal discomfort to the patient, we became interested in determining whether massive therapy with this agent would be practical.

The Present Study

Material and Methods.—In this study, 500,000-unit compressed tablets of penicillin V and 200,000-unit compressed tablets of potassium penicillin G were employed throughout. Penicillin determinations were performed by the cup-plate method with Sarcina lutea as the test organism.[5] Standard curves were determined with penicillin V assayed at 1,630 units per milligram and potassium penicillin G assayed at 1,560 units per milligram. A standard curve was determined with each group of unknowns. The blood penicillin determinations were all made on specimens of serum. The serum was stored at –20 C until determinations were done. No serum samples were stored longer than two weeks.

Results of Pharmacological Studies.—Eight normal fasting adults were given a single 2 million-unit dose of penicillin V orally, and penicillin blood concentrations were determined after one-half, one, two, three, and four hours. Forty-eight hours later the study was repeated under the same conditions except that penicillin G was employed. The results are presented in table 1. These data indicate that after half an hour, penicillin G produced somewhat higher serum concentrations than did penicillin V. However, the average levels were higher one through four hours after administration of penicillin V. This difference was especially notable from the second through the fourth hours, when penicillin V resulted in average serum levels from 1.7 to 2.8 times as great as penicillin G. It is also noted that penicillin V produced higher serum concentrations in each individual during this period.

Four patients were given 2 million units of penicillin V by the oral route daily at four-hour intervals (2, 6, and 10 a. m. and 2, 6, and 10 p. m.) for six weeks. Penicillin blood concentrations were determined at various hours during the day and night throughout the six-week period in two of the four patients. The other two patients also received streptomycin at some time during their course of therapy. Penicillin levels were not determined during the period when these patients were receiving combined therapy. At the conclusion of the therapy with penicillin V, three of the four patients were given penicillin G for three days on an identical schedule. The results of the determinations are summarized in table 2 and figures 1 and 2.

It can be seen from table 2 that concentrations of penicillin V ranged from 2.4 to 20 units per milliliter of serum, while penicillin G concentrations ranged from 1.2 to 12.0 units. It is apparent that the average levels of penicillin V were considerably greater than those of penicillin G. Figure 1 is derived from average values for penicillin V. This figure illustrates the average degree of penicillinemia observed in the normal subjects after a single 2 million-unit dose and in the group of patients who received multiple doses consisting of 2 million units every four hours. It is obvious that average serum penicillin concentrations were considerably greater in

2. McDermott, W., and others: Absorption, Excretion, and Destruction of Orally Administered Penicillin, J. Clin. Invest. **25**: 190, 1946.

3. (*a*) Behrens, O. K., and others: Biosynthesis of Penicillins: IV. New Crystalline Biosynthetic Penicillins, J. Biol. Chem. **175**: 793, 1948. (*b*) Behrens, O. K., and Kingkade, M. J.: Biosynthesis of Penicillins: VIII. Studies with New Biosynthetic Penicillins on Penicillin Resistance, ibid. **176**: 1047, 1948. (*c*) Brandl, E.; Giovannini, M., and Margreiter, H.: Untersuchungen über das säurestabile, oral wirksame Phenoxymethyl-Penicillin (Penicillin V), Wien. med. Wchnschr. **103**: 602, 1953. (*d*) Brandl, E., and Margreiter, H.: Ein säurstabiles biosynthetisches Penicillin, Oesterr. Chem.-Ztg. **55**: 11, 1954. (*e*) Giovannini, M.: Vergleichende Untersuchungen von Penicillin G und Penicillin V nach oraler Verabreichung, Wien. med. Wchnschr. **104**: 910, 1954. (*f*) Brunner, R.: Die biologische Testung des Penicillin V (Phenoxymethyl penicilliin), Scientia Pharmaceutica **22**: 151, 1954.

4. (*a*) Footnote 3c. (*b*) Footnote 3e. (*c*) Wright, W. W., and others: Serum Concentrations and Urinary Excretion Following Oral Administration of Penicillin V and Comparison with Penicillin G, Antibiotic Med. **1**: 490, 1955. (*d*) Martin, W. J.; Nichols, D. R., and Heilman, F. R.: Penicillin V, a New Type of Penicillin: Preliminary Clinical and Laboratory Observations, Proc. Staff Meet. Mayo Clin. **30**: 467, 1955.

5. Grove, D. C., and Randall, W. A.: Assay Methods of Antibiotics: A Laboratory Manual, New York, Medical Encyclopedia, Inc., 1955, pp. 14-16.

the group that received multiple doses. Although Martin and co-workers [4d] were unable to demonstrate penicillin "pile-up" when they gave 400,000 units of penicillin V orally every four hours for periods up to 120 hours, our data suggest that augmentation may occur when larger doses are utilized, i. e., 2 million units every four hours for prolonged periods.

TABLE 2.—*Comparison of Blood Penicillin Concentration in Four Patients After Oral Administration of Two Million Units of Penicillin V and Penicillin G Every Four Hours for Prolonged Periods*

	Time After Administration, Hr.				
	½	1	2	3	4
Penicillin V					
Range	4.1-18.27*	2.4-17.7	5.2-20.0	4.7-13.15	2.5-10.4
Av. range	8.75	8.24	6.67	8.07	5.34
Specimens, no.	7	13	19	8	27
Penicillin G					
Range	1.56-10.4	2.58-12.0	2.9-5.04	1.2-5.4	1.27-4.8
Av. range	4.40	5.71	3.33	3.33	2.42
Specimens, no.	4	4	4	4	4

* Values expressed as units per milliliter of serum.

Figure 2 is a composite. Each reference point on the chart is an average of several determinations at that particular time in each of the four patients who received 12 million units of penicillin V orally every day for six weeks. It can be seen that significant serum penicillin concentrations were maintained throughout the 24-hour period.

Report of Cases

CASE 1.—A 64-year-old man was admitted to the Henry Ford Hospital on July 29, 1955. He had experienced anorexia, fever, mental confusion, and chilly sensations for one week prior to admission. For two days he had noted pain in the left anterior chest, back, shoulder, and left arm. His history disclosed a known heart murmur since the age of 21 years. In 1945 he had experienced an episode of crushing substernal chest pain associated with nausea and dyspnea. He was hospitalized at another hospital during this illness. In 1948 he had a sudden onset of hemiplegia on the right side that cleared slowly. He was first admitted to the Henry Ford Hospital in March, 1954. At this time he complained of weight loss, increasing fatigue, dyspnea, and ankle edema for the year prior to hospitalization. Examination revealed mitral stenosis, mitral insufficiency, auricular fibrillation, and congestive heart failure. His condition was fairly well controlled with administration of digitalis and mercurial diuretics and restriction of salt intake.

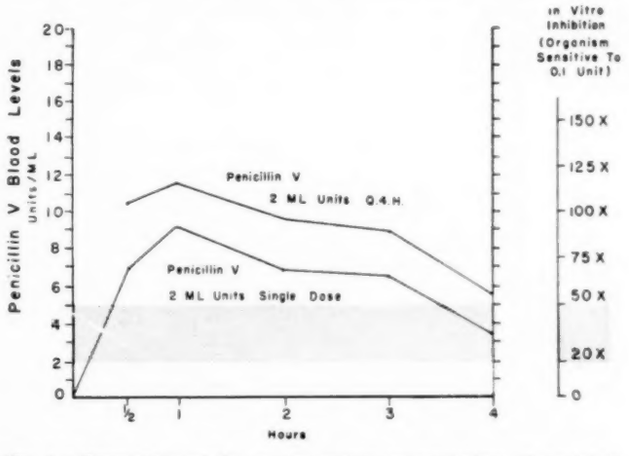

Fig. 1.—Comparison of the average serum concentrations of penicillin after a single 2 million-unit dose of penicillin V and multiple doses consisting of 2 million units every four hours.

He was admitted to the Henry Ford Hospital for the second time on Feb. 5, 1955, because of sudden onset of hemiplegia on the right side. At this time he was treated with anticoagulants in addition to digitalis, mercurials, and salt restriction. There was progressive clearing of the hemiparesis, so that by March 21 there was no residual paralysis. Physical examination on admission revealed that the patient's temperature was 39 C (102.2 F) and his pulse rate was 120 per minute and grossly irregular. There were 24 respirations per minute, and his blood pressure was 120/80 mm. Hg. He was emaciated and appeared acutely and chronically ill. He was disoriented as to time, place, and person. He was not dyspneic. The heart was markedly enlarged to the left, and the rhythm was totally irregular. At the apex, a grade 3 systolic murmur transmitted to the left axilla and a localized rumbling diastolic murmur were heard. There were moist rales at both lung bases. The liver edge was tender and palpable 6 cm. below the right costal margin. The spleen was not felt. No skin lesions were noted, and there was no dependent edema. Except for the mental confusion, the neurological examination was negative.

Laboratory findings were as follows: The hemoglobin level was 12.7 gm. per 100 cc., and there were 4,500,000 red blood cells and 13,600 white blood cells per cubic millimeter. There were 69% neutrophils, 24% lymphocytes, and 7% monocytes on differential count. The urinalysis revealed a specific gravity of 1.011, no sugar or albumin, and three to four red blood cells and an occasional white blood cell per high-power field. The sedimentation rate was 31 mm. per hour (Wintrobe). Results

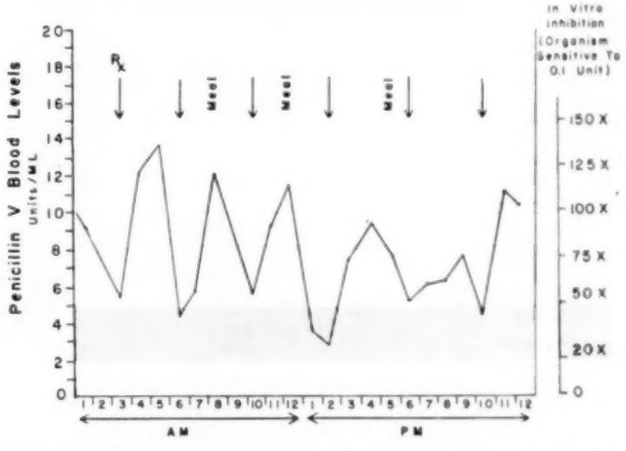

Fig. 2.—Penicillin V concentrations in the serum after administration of multiple doses consisting of 2 million units given orally every four hours in four patients.

of an electrocardiographic study were consistent with right bundle-branch block and auricular fibrillation. Marked generalized cardiac enlargement and congestive changes in the lungs were noted on x-ray studies of the chest. Three blood cultures were positive for microaerophile alpha-hemolytic streptococci.

The patient's course is summarized in figure 3. Three blood cultures were obtained, and therapy with 400,000 units of "fortified" procaine penicillin G every six hours was started. He had received a total dose of 4,800,000 units by the fourth hospital day. At this time all three blood cultures were reported as positive for alpha-hemolytic streptococci. In vitro sensitivity studies indicated that growth of the organism was inhibited by 0.081 units of penicillin V per cubic millimeter. Parenteral administration of penicillin G was discontinued, and oral therapy with 12 million units a day (2 million units every four hours) of penicillin V was instituted. During the first five days of treatment the temperature fell steadily from 39.2 C (102.6 F), reaching normal on the sixth day. The cardiac rate rapidly decreased to 80 per minute, and by the sixth hospital day the mental confusion had subsided, the lungs had cleared, and the liver had decreased in size. Daily examinations failed to reveal petechial hemorrhages, and the spleen could not be palpated. Blood cultures taken triweekly remained sterile. Throughout the course of therapy, nonfasting serum penicillin concentrations obtained two and four hours after the patient's taking the dose ranged from 2.9 to 25.6 units per millimeter. The patient was treated

for a total of 42 days. He has been followed for four months since the completion of therapy. Blood cultures have remained sterile, and cardiac compensation has been maintained.

CASE 2.—An 18-year-old man was admitted to the Henry Ford Hospital on Sept. 14, 1955. Three and one-half weeks prior to admission he had developed a toothache and was found to have a deeply carious tooth, without evidence of apical abscess. He was given 300,000 units of procaine penicillin G with 0.25 gm. of streptomycin sulfate and 0.25 gm. of dihydrostreptomycin sulfate one hour preoperatively, and the tooth was extracted. For the next 5 days, 200,000 units of penicillin G was given orally three times daily, followed by 200,000 units twice daily for 10 additional days. One week before admission he noted the onset of fever, with temperature of up to 39.7 C (103.5 F) accompanied by mild malaise. This persisted until Sept. 12, when he presented himself to the outpatient clinic and a blood culture was drawn.

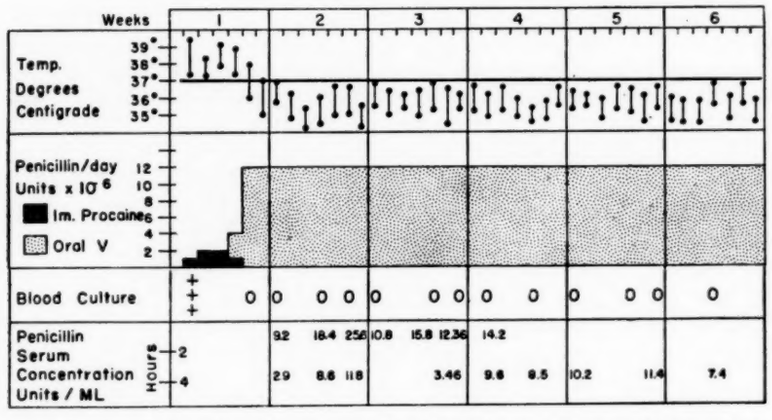

Fig. 3.—Course of patient with subacute bacterial endocarditis due to alpha-hemolytic streptococci (case 1).

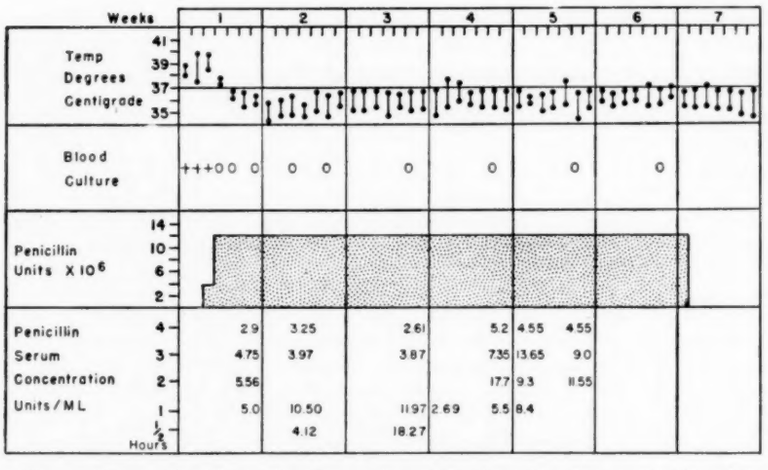

Fig. 4.—Course of patient with subacute bacterial endocarditis due to alpha-hemolytic streptococci (case 2).

His history disclosed a known heart murmur since the age of 6 months. At the age of 10 he developed daily fever, with temperature ranging from 37.8 to 39.5 C (100 to 103 F) and a cough that persisted for 10 months. He was first admitted to the Henry Ford Hospital on July 23, 1947, with this complaint. Numerous blood cultures were sterile. A diagnosis of bacterial endocarditis without bacteremia was made, and he was treated with 100,000 units of aqueous penicillin, administered intramuscularly every three hours for 50 days. He was asymptomatic until Jan. 27, 1954, when he developed fever, chills, cough, and migratory arthralgia. Numerous blood cultures were sterile. A diagnosis of bacterial endocarditis without demonstrable bacteremia was made, and he was treated with 4 million units of aqueous penicillin and 1 gm. of streptomycin daily for four weeks. He became afebrile and asymptomatic. On April 10, 1954, he was admitted for the third time with recurrence of fever. Again blood cultures were sterile, and he received tetracycline orally for 21 days with prompt remission of fever. Data obtained from cardiac catheterization in January, 1955, were consistent with a diagnosis of infundibular pulmonary stenosis.

Physical examination revealed that his temperature was 40 C (104 F), his pulse rate 100 per minute, and respiration rate 24 per minute. The blood pressure was 110/70 mm. Hg. He appeared moderately ill, with a flushed face. No petechial hemorrhages were noted. The heart was not enlarged to percussion. The rhythm was regular. A grade 4 harsh systolic murmur was audible along the left sternal border, loudest at the third left interspace. A systolic thrill was palpable in this area. The pulmonic second sound was absent. No diastolic murmur was heard. The spleen was not palpable.

Laboratory tests revealed that the hemoglobin level was 15.9 gm. per 100 cc., and there were 5,950,000 red blood cells and 9,700 white blood cells per cubic millimeter. There were 82% neutrophils, 12% lymphocytes, 5% monocytes, and 1% basophils. The urinalysis was negative. Roentgenogram of the chest disclosed slight prominence of the left cardiac border. Three blood cultures obtained during the first two days of hospitalization were positive for alpha-hemolytic streptococci. The organism was sensitive in vitro to 0.04 units of penicillin per cubic milliliter. The patient's course is shown in figure 4. He was given 2 million units of penicillin V orally every four hours for six weeks. His temperature fell to normal on the second day of treatment, and his symptoms subsided promptly. Biweekly blood cultures made during treatment and for one month after discontinuing therapy with penicillin remained sterile. The patient has been followed for three months since completion of therapy, and there has been no clinical or bacteriological evidence of relapse.

CASE 3.—A 16-year-old girl was admitted to the Henry Ford Hospital on Aug. 17, 1955. She had experienced daily chills and fever associated with headaches, malaise, sore throat, nausea, and vomiting for eight days. Six days prior to admission she noted swelling and pain in the left ankle that persisted for four days. Five days prior to admission she noted a bluish tender area on the palmar surface of the tip of the left middle finger. She received an indefinite amount of penicillin both orally and by injection during the eight days prior to admission to the hospital. Her history revealed the presence of a heart murmur since an attack of rheumatic fever at the age of 11 years. In May and June, 1955, the patient was seen on two occasions with attacks of supraventricular tachycardia that subsided spontaneously. A diagnosis of inactive rheumatic heart disease with mitral stenosis and insufficiency was made at that time.

Physical examination revealed that her temperature was 41.2 C (106.2 F) and that pulse rate was 120 per minute and regular. There were 20 respirations per minute, and the blood pressure 115/64 mm. Hg. She was a well-developed and well-nourished young female and appeared acutely ill. There was a single bluish tender lesion, 6 mm. in area and slightly elevated, on the tip of the left middle finger. Several palpebral conjunctival and subungual petechial hemorrhages were present. The heart was enlarged to the left, the point of maximal impulse being in the left sixth interspace 11.5 cm. from the midsternal line. The precordium was heaving, and a diastolic thrill was noted at the apex. A grade 4 harsh, high-pitched systolic murmur and an apical diastolic rumble were heard on auscultation. The spleen tip was palpable 4 cm. below the left coastal margin. The remainder of the physical examination was negative.

Laboratory tests revealed that the hemoglobin level was 11.4 gm. per 100 cc.; there were 3,600,000 red blood cells and 15,760 white blood cells per cubic milliliter. There were 73% polymorphonuclear leukocytes, 22% lymphocytes, and 4% monocytes. The sedimentation rate was 41 mm. per hour (Wintrobe), and the hematocrit was 37%. The urine was normal except for a trace of albumin. An electrocardiogram disclosed evidence of left ventricular enlargement. Cardiac fluoroscopy showed left

auricular enlargement. Seven blood cultures taken on the third and fourth hospital days were all positive for an organism identified as Neisseria sicca. The organism was inhibited in vitro by 2.5 units of penicillin per cubic milliliter or by less than 0.56 units of penicillin combined with 5 mcg. of streptomycin per cubic milliliter.

The patient's course is shown in figure 5. On the fourth hospital day, intramuscular administration of one million units of procaine penicillin twice daily was started. On the sixth hospital day parenteral administration of penicillin was discontinued and oral administration of 2 million units of penicillin V every four hours was begun. Within 48 hours of the initiation of penicillin therapy the patient became afebrile and showed marked symptomatic improvement. The tachycardia decreased, and the systolic murmur decreased in intensity. On the 15th day of treatment she developed a headache and her temperature rose to 40.4 C (104.5 F). New petechial hemorrhages were noted on the soft palate and in the conjunctiva. During the ensuing four days her temperature remained elevated, although blood cultures obtained at this time were all sterile. The results of the in vitro sensitivity test became available at this time, and 0.5 gm. of streptomycin plus 0.5 gm. of dihydrostreptomycin given intramuscularly twice daily was added to the course of therapy. She promptly became afebrile, and no new petechiae were noted. The combined therapy was continued for six weeks. Frequent blood cultures during treatment and twice weekly for one month after treatment was discontinued were sterile. The patient was last seen 11 weeks after cessation of treatment and has maintained clinical and bacteriological remission.

CASE 4.—A 30-year-old man was first admitted to the Henry Ford Hospital on June 16, 1955. Two years prior to admission the patient had noted exertional dyspnea and easy fatigability. Six months before admission there was an increase in these symptoms associated with progressive weight loss of 20 lb. (9.1 kg.). Three weeks prior to admission the patient developed fever, nausea, vomiting, and pain in the left side of the chest, and one week later he was admitted to another hospital. At this time physical examination revealed a loud systolic murmur and an associated systolic thrill at the base of the heart. There was dulness to percussion and decreased intensity of breath sounds over the posterior base of the left lung. The patient was treated with penicillin and two weeks later transferred to the Henry Ford Hospital.

At the time of admission, the patient was afebrile, the blood pressure was 110/82 mm. Hg, and he did not appear acutely ill. Significant physical findings were essentially as previously described. Results of a complete blood cell count, urinalysis, and serodiagnosis were normal. Seventy-five cubic centimeters of sterile straw-colored fluid was removed from the left pleural space. An electrocardiogram indicated complete right bundle-branch block and first-degree heart block. Cardiac catheterization performed on the fourth hospital day provided data that were compatible with the diagnosis of intra-auricular septal defect. The septal defect was surgically repaired by Dr. Conrad Lam on the 11th hospital day. Postoperatively, the patient ran a low-grade fever, with temperature ranging from 37.6 to 38 C (99.7 to 100.4 F), until the 14th postoperative day, when the temperature became normal. The patient received 400,000 units of aqueous procaine penicillin daily while he was febrile. He was discharged asymptomatic on Aug. 2, 47 days after hospital admission.

On Aug. 22 (56 days after operation), the patient was readmitted for postoperative cardiac catheterization. Physical examination at this time revealed a well-healed right thoracotomy scar, a harsh grade 4 systolic murmur best heard in the second and third costal interspaces just to the left of the sternum, and dulness to percussion and slight decrease in breath sounds over the lower two-thirds of the left posterior chest. Laboratory tests revealed that the hemoglobin level was 12.2 gm. per 100 cc., and there were 4 million red blood cells and 5,500 white blood cells per cubic milliliter. There were 62% neutrophils, 32% lymphocytes, 3% monocytes, 2% eosinophils, and 1% basophils on differential count. Results of urinalysis were negative. The sedimentation rate was 34 mm. per hour (Wintrobe), and the hematocrit was 40%. The patient's course is shown in figure 6. On the third hospital day, before cardiac catheterization was done, the patient experienced a shaking chill followed by a rise in temperature to 39.8 C (103.6 F). Results of the physical examination at this time were essentially unchanged. Three blood cultures were obtained during the ensuing 36 hours, and administration of 300,000 units of procaine penicillin and 0.25 gm. each of streptomycin and dihydrostreptomycin twice a day was started. A total of three doses had been given when one of the three blood cultures yielded alpha-hemolytic streptococci that were inhibited in vitro by 0.03 units of penicillin per cubic milliliter. A nonhemolytic Micrococcus pyogenes var. albus that failed to coagulate human plasma was later isolated from the remaining cultures. The latter organism was considered at the time to represent a contaminant. On the fifth hospital day, on the assumption that penicillin-sensitive alpha-hemolytic streptococci represented the offending organism, the procaine penicillin–streptomycin-dihydrostreptomycin therapy was discontinued and oral administration of 12 million units of penicillin V daily was instituted. The temperature rapidly became normal and remained so for the next five days. From the 8th to the 13th days of treatment the patient developed recurrence of daily temperature elevations. Multiple blood cultures obtained during this period remained sterile. On the 13th day of therapy administration of 1 gm. of equal parts of streptomycin and dihydrostreptomycin twice daily was added to the program. The temperature again became normal. Four weeks later, administration of streptomycin and dihydrostreptomycin was discontinued uneventfully. Therapy with penicillin V was discontinued two weeks later, or six weeks after the last day on which he had a fever. Frequent blood cultures that were made during treatment and for two weeks thereafter remained sterile, and the patient was discharged to the outpatient department for subsequent follow-up on Oct. 25.

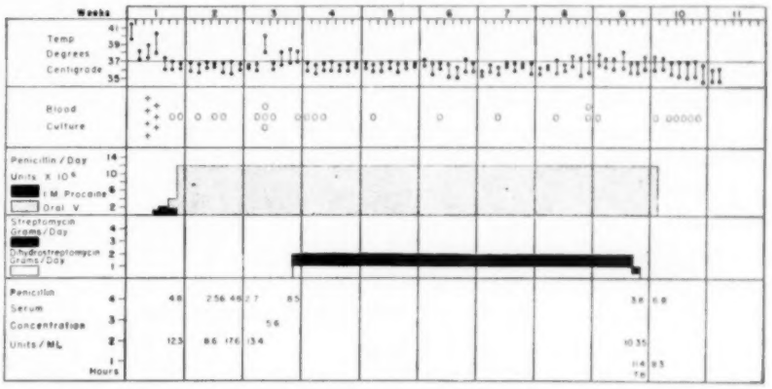

Fig. 5.—Course of patient with subacute bacterial endocarditis due to Neisseria sicca (case 3).

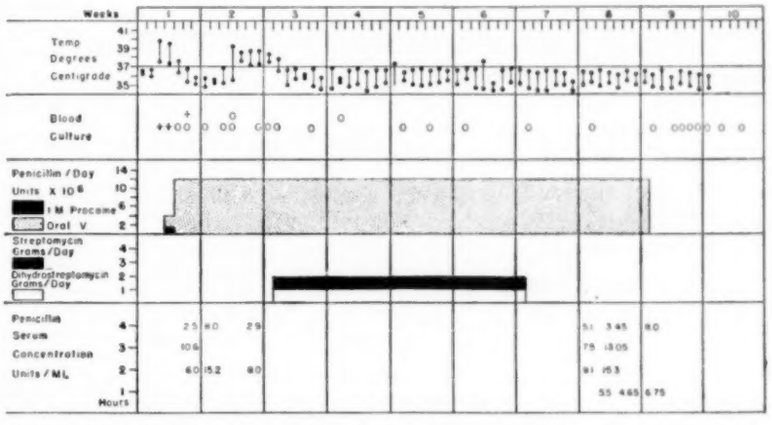

Fig. 6.—Course of patient with subacute bacterial endocarditis due to Micrococcus pyogenes var. albus (case 4).

On Nov. 12, 1955, M. pyogenes var. albus was again isolated from the blood, and during the ensuing 10 days repeated blood cultures were positive for this organism. In view of these findings, the patient was readmitted to the hospital. The Micrococcus isolated on Nov. 12 was resistant in vitro to more than 12.5 units of penicillin V per cubic milliliter. At the time of this report, clinical and bacteriological relapse has occurred subsequent to a four-week course of combined therapy with chloramphenicol, streptomycin, and erythromycin.

Comment

The chemotherapy of serious infections such as subacute bacterial endocarditis requires a prolonged high-dosage regimen. Parenterally administered penicillin in such a therapeutic program is not infrequently associated with poor patient tolerance, local thrombophlebitis, and inflammatory reactions. It would appear that these complications of parenteral therapy could be conveniently avoided through the oral use of penicillin. However, the oral administration of penicillin in the treatment of bacterial endocarditis has not been advocated because of the reported unpredictability and low order of absorption of this agent from the gastrointestinal tract. When penicillin V given orally was reported to produce substantial blood penicillin levels, our attention was directed to the possibility of developing a high oral dosage program that would be satisfactory for the treatment of bacterial endocarditis in selected cases.

In these studies, it has been demonstrated that blood penicillin concentrations two, three, and four hours after an oral dose of 2 million units of penicillin V were definitely superior to those obtained after a comparable oral dose of penicillin G. This observation was true when either a single or a continuous multiple dosage scheme was employed. Serum concentrations after continuous multiple dosage of penicillin V were of greater magnitude than those that were observed after a single dose, and this fact suggested that some degree of accumulation had occurred. When 2 million units of pencillin V was administered orally every four hours, there was a significant degree of penicillinemia throughout the 24-hour period. Our data are in agreement with those recently reported by White and co-workers.[6] These same investigators also demonstrated that, when 2 million units of penicillin V is administered orally every four hours, serum penicillin concentrations are similar to those observed after the intramuscular administration of 1,200,000 units of aqueous procaine penicillin G every six hours. Since others have shown that selected cases of subacute bacterial endocarditis may be adequately treated with aqueous procaine penicillin alone or in combination with streptomycin, it does not seem unreasonable to assume that orally administered penicillin V, either alone or in combination with streptomycin, should also be effective.

Four patients with subacute bacterial endocarditis have been treated. In two instances the causative organisms were penicillin-sensitive alpha-hemolytic streptococci. Both of these patients received 12 million units of penicillin V orally every day for six weeks and have exhibited a satisfactory clinical and bacteriological response. An unusual organism was isolated in the third case, and it was found to be resistant in vitro to penicillin alone but moderately sensitive to a combination of penicillin and streptomycin. The patient in this case was treated with combined orally given doses of penicillin V and intramuscularly given doses of streptomycin. The clinical result was again good, and remission has been maintained. In the fourth patient, remission could not be maintained. In retrospect, the offending organism would appear to have been a penicillin-resistant Micrococcus from the beginning. Certainly, this type of treatment was not indicated in this instance.

The relative toxicity of penicillin G and V given orally has not been adequately studied.[7] Prolonged administration of high oral doses of penicillin V did not result in toxic gastrointestinal manifestations in the patients studied. From the foregoing data, it seems that penicillin V, given orally, may have a place in the treatment of bacterial endocarditis due to penicillin-sensitive organisms. Probenecid, a renal blocking agent, has been shown to markedly increase blood penicillin V levels,[6] and the use of this agent in conjunction with penicillin V offers another approach to the problem of massive oral therapy in serious infections.

2799 W. Grand Blvd. (2) (Dr. Quinn).

6. White, A. C., and others: Absorption and Antimicrobial Activity of Penicillin V (Phenoxymethyl Penicillin), in Antibiotics Annual 1955-56, New York, Medical Encyclopedia, Inc., 1956, pp. 490-500.

7. Jones, W. F., and Finland, M.: Blood Levels from Orally Administered Penicillins G and V: Relation to Food Intake, New England J. Med. **253**: 754, 1955.

Ménière's Disease.—The etiology of Ménière's disease is not proved but good evidence suggests that it is a vasomotor neurosis like acrocyanosis, Raynaud's disease, migraine, angioneurotic edema, urticaria, and other specific and physical allergies. A tendency for the peripheral vascular bed to react abnormally to various types of stress such as emotional perturbation, fatigue, atmospheric and weather changes, sunlight, and nontoxic protein substances is characteristic of this group of conditions. The pathologic picture seen in the capillaries of such individuals under biomicroscopy is a spasm of the "lock muscle" at the beginning of the metarteriole with constriction of the arterial limb of the capillary loop and dilation and varicosity of the venous limb which is refluxly filled with blood. The result is a tendency toward cyanosis. This in turn appears to lead to cellular injury of the capillary endothelium and of the leukocytes and erythrocytes contained in the capillary loop. The endothelial injury leads to intravascular agglutination, known as blood sludge, and increased permeability of the capillary wall. The injury to the leukocytes leads to the release of histamine and other toxic products which also increase capillary permeability. This greater capillary permeability leads to the collection of interstitial fluid of increased osmotic pressure. This condition is considered to depend on disintegration of the autonomic nervous control of cholinergic type. When this reaction involves the mechanism secreting endolymph, then quantity and osmotic pressure of the endolymph secreted increase and the resultant endolymphatic hypertension produces characteristic pathologic picture dilation of the ductus cochlearis. The attacks of vertigo are thought to be due to spasm of the end arterioles of the vestibular artery which supply the nerve cells of the crista and macula, and the fluctuations in auditory threshold are thought to be due to pressure on the hair cells of the organ of Corti and to changes in electrolyte balance in the endolymph, especially to loss of potassium. The recruitment and diplacusis appear to be caused by edema of the tectorial membrane. All successful medical treatment of Ménière's disease has been based on the hypothesis that it is an instance of autonomic imbalance of the cholinergic type.—Henry L. Williams, M.D., The Medical Treatment of Ménière's Disease, *Geriatrics*, January, 1956.

NEONATAL HEPATITIS IN SIBLINGS

REPORT OF TWO CASES WITH GIANT MULTINUCLEATED LIVER CELLS AND FATAL TERMINATION

Philip Krainin, M.D.
and
Bernard Lapan, M.D., New York

• Two infants, one male, the other female, died 6½ and 45 hours after birth. Antemortem findings were chiefly hemorrhagic. The essential postmortem findings were severe inflammatory and degenerative changes in the liver.

Liver biopsy and function tests in the mother showed that her liver was similarly involved. Unusual sensitivity to diethylstilbestrol and infection with a virus were considered as factors in the etiology, but the resemblance of these cases to erythroblastosis suggested the possibility that the bloods of the parents might have been incompatible. Tests failed to reveal incompatibility as to the Rh and A-B-O factors. It is suggested that the incompatibility might be of some rare or unknown type.

Recent experiences with the occurrence of unusual neonatal deaths in two siblings, with severe hepatitis, cirrhosis, large multinucleated giant cells, and marked deposition of iron in the liver, prompt this report. Both siblings exhibited hemorrhagic phenomena prior to death, one showing severe subarachnoid hemorrhage and the other gastrointestinal and subcutaneous bleeding. There is a growing body of literature [1] describing fetal and neonatal hepatitis and cirrhosis with similar histological changes. Two main etiological categories have been emphasized. A transplacental viral factor has been postulated by Stokes,[2] Craig and Landing,[1a] Dible,[1b] and others.[3] Blood group incompatibility has been emphasized by Reiffenstuhl,[4] Zollinger,[5] and others.[6] These conditions have been variously described as "viral hepatitis," "fetal hepatitis," and "neonatal hepatitis." The presence of similar severe liver disease and fatal outcome in three siblings has been described by Dible.[1b] Our two cases make a total of five such known instances, with no demonstrable blood group incompatibility, occurring in siblings. Other etiologies for similar cases of severe fetal and neonatal liver disease have been described in the literature; namely, syphilis, congenital biliary atresia, toxic agents (arsenic, chloroform, cinchophen), and nutritional deficiency (as seen in kwashiorkor), none of which seem to have any bearing on our cases or those of Dible. An additional unusual finding in our two cases was the evidence of liver damage in the mother as shown by liver function tests. It is also, to our knowledge, the first reported instance of abnormal liver biopsy findings in mothers of such infants.

Report of Cases

CASE 1.—The mother was a 26-year-old, para 3, gravida 4, woman when first seen by one of us (B. L.) in November, 1951. Her history included the usual childhood illnesses but no scarlet fever or renal disease. There were no previous operations, and her menstrual cycle was normal. The family history was negative for tuberculosis, diabetes, and malignant diseases. Neither she nor her husband had ever had syphilis. There was no history of exposure at any time to alcohol, heavy metals, chloroform, or other toxic substances. She never had been jaundiced nor had any transfusions. Her first pregnancy had terminated in January, 1950, with a full-term breech delivery at another hospital. The infant died two days after delivery, and postmortem examination revealed pulmonary atelectasis. The liver was normal histologically. (Sections were reviewed for the purpose of this report.) Her second pregnancy ended in September, 1950, with a spontaneous abortion at three months of gestation. Her third pregnancy terminated at eight months; the infant died six and one-half hours after delivery (case 2). In a preconceptional study, done in November and December, 1951, the mother's basal metabolic rate was −11% and examination of her husband's seminal fluid revealed no abnormalities. Hysterograms revealed several small filling defects in the endometrial cavity, for which curettage was performed at Lebanon Hospital on Dec. 17, 1951. The surgical pathological report showed cyclic endometrial hyperplasia in a proliferative stage. The patient conceived again in March, 1952. Because of her previous history of spontaneous and threatened abortions, she was given thyroid extract (Proloid) 2 grains (0.13 gm.), daily, and diethylstilbestrol (Stilbestrol), 5 mg. daily. Two episodes of mild vaginal bleeding occurred in May and June, so that the diethylstilbestrol dosage was gradually increased to 250 mg. daily. Her blood pressure ranged from 120/60 to 130/90 mm. Hg. Albuminuria appeared in the fifth month of pregnancy in amounts varying from 1 to 3+; this had not been present prior to pregnancy and disappeared at its termination. There were no casts, red blood cells, or white blood cells on microscopic examination of the urine. There was no edema or jaundice at any time.

On Dec. 4, 1952, she was delivered by one of us (B. L.) at Lebanon Hospital, after one and one-half hours of labor, of a full-term female infant, weighing 5 lb. 9 oz. (2,523.11 gm.). The liquor amnii was not stained. The placenta appeared normal. No abnormalities of the infant's heart, lungs, or abdomen were noted on clinical examination. There were no apparent

From the Lebanon Hospital.

Blood group analyses of the parents in case 1 were done by Dr. S. Dresner, Lebanon Hospital, and Dr. P. Levine, Ortho Research Foundation.

Pathological findings at autopsy (case 1) were made by Drs. J. C. Ehrlich and I. M. Ratner, Lebanon Hospital.

Drs. R. Koenig and A. Schwarz, Jewish Memorial Hospital, New York, supplied the data for case 2.

This study was aided by a grant from the Aaron W. Davis Foundation.

1. (*a*) Craig, J. M., and Landing, B. H.: Form of Hepatitis in Neonatal Period Simulating Biliary Atresia, A. M. A. Arch. Path. **54**: 321 (Oct.) 1952. (*b*) Dible, J. H., and others: Fœtal and Neonatal Hepatitis and Its Sequelae, J. Path. & Bact. **67**: 195, 1954. (*c*) Stokes, J., Jr.; Wolman, I. J.; Blanchard, M. C., and Farquhar, J. D.: Viral Hepatitis in the Newborn: Clinical Features, Epidemiology and Pathology, Society Transactions of the Sixty-First Annual Meeting of the American Pediatric Society, A. M. A. Am. J. Dis. Child. **82**: 213 (Aug.) 1951.

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5. Zollinger, H. U.: Die biliäre leberzirrhose im Säuglings—und Kleinkindalter und ihre Beziehung zum Morbus haemolyticus neonatorum, Helvet. paediat. acta (supp. 2) **1**: 104, 1946.

6. Zeitlhofer, J., and Speiser, P.: Diffuse intraacinäre Lebercirrhose und Hydrops congenitus bei Rh.-Incompatibilität, Oesterr.Btschr. Kinderh. **5**: 217, 1950.

congenital anomalies. Seventeen hours after birth, a small amount of blood-tinged vomitus appeared. Mild icterus and a small purpuric area on the left thigh were then noted. The baby had been taking feedings well. On the day after delivery, the stool contained meconium mixed with bright red blood. Examination of the infant's blood showed a hemoglobin level of 12 gm. per 100 cc. (photoelectric colorimetric method). The red blood cell count was 3,500,000 per cubic millimeter, with

Fig. 1.—Undersurface of liver showing coarse nodules of infant in case 1.

30% polymorphonuclear cells, 46% band cells, 20% lymphocytes, and 4% monocytes. The platelets appeared normal. No nucleated red blood cells were seen on smear. The Coombs test was negative. The blood group was A, Rh positive. There were no chemical examinations of the blood. The infant was given 50 cc. of compatible group A, Rh-positive blood and 35 cc. of 5% dextrose in water. The next day, her condition seemed to deteriorate. She was lethargic, refused feedings, and regurgitated bloody material. Stools continued to show gross blood. Cyanosis, twitchings and a cerebral cry appeared. The infant died on Dec. 6, 1952, 45 hours after birth.

The important pathological findings at autopsy included a distinct icteric tint of the skin and scleras. Small areas of ulceration and hemorrhage in the mucosa of the esophagus, stomach,

TABLE 1.—*Summary of Liver Function Tests Performed in 1953 on Mother of Infant in Case 1*

Date	Cephalin Flocculation	Cholesterol, Mg./100 Cc.	Cholesterol Esters, Mg./100 Cc.	Plasma Protein, Gm./100 Cc.		
				Total	Albumin	Globulin
March 13	2+	...	...	...	...	...
March 17	4+	...	...	...	...	...
March 21	4+	...	...	...	...	...
April 7	...	264	114	7.0	3.3	3.7
May 16	...	278	81	6.8	2.2	4.6
May 19	4+	...	...	...	...	...

and rectum were noted. The liver (fig. 1) was reduced in size (40.1 gm.) and tan in color, and all surfaces were irregularly studded with nodules, some of which were green. The consistency of the liver was markedly increased, and the cut surface did not show normal parenchymal markings. No abnormality of the gallbladder, biliary tree, or hepatic vessels was demonstrated. On section, the basal ganglions presented a distinct uniform and symmetrical bright yellow discoloration typical of kernicterus.

Microscopic study of the liver (fig. 2) showed striking transformation of the normal pattern, the most outstanding being the large syncytial cytoplasmic masses of extremely irregular size, shape, and distribution, each containing as many as 40 nuclei. The cell boundaries were not distinguishable but appeared to be continuous with a few remaining normal hepatic cords. In addition, increased fibrillar connective tissue, infiltrated by inflammatory cells, and aggregates of immature blood cells, predominantly undifferentiated forms (extramedullary hemopoiesis) were found. The cytoplasm of many of the multinucleated giant cells contained finely granular rich brown pigment, which was iron positive (Prussian blue method). Complete details and a discussion of the gross and microscopic autopsy findings are reported elsewhere.

During the months following the death of this infant a series of tests of liver function was carried out on the parents (table 1). Those on the mother showed the cephalin flocculation test was 4+ on three occasions, the total cholesterol was normal but the esters ranged between 30 and 35%, and the total serum protein level was normal with a reversal of the albumin-globulin ratio. Those on the father were normal. On April 24, 1953, a specimen of the mother's liver was obtained by needle biopsy. The microscopic report revealed moderate but distinct variation in the size of the nuclei of hepatic cells (fig. 3). Occasional nuclei were small and hyperchromatic; others were, large and "ballooned." A rare binucleated cell was observed. There was no evidence of bile stasis. The cytoplasm of the hepatic cells was finely granular and stippled with light brown bile pigment. A rare cell showed basophilic smudging of the cytoplasm. There was no coarse cytoplasmic vacuolation or reticulation. The Kupffer cells appeared normal. There was no inflammatory infiltrate. Stain for iron-containing pigment was negative. The findings showed grade 1+ liver cell damage.[7] The results are shown in table 2. The Coombs test on the mother was negative for atypical antibodies. Tests of both bloods for antigenic components indicated that the mating was incompatible for **S, Kell, Le_a,** and **P** factors, but there were no demonstrable antibodies for these factors (table 2).

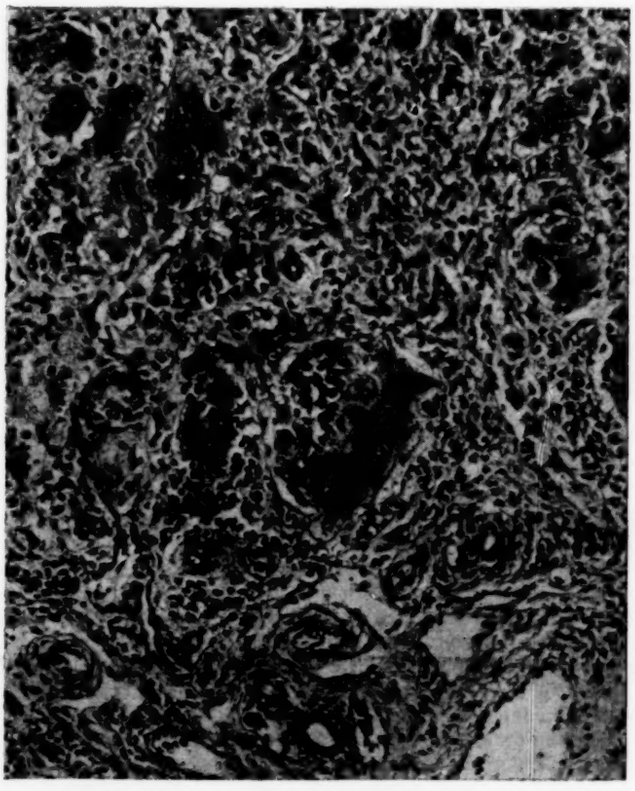

Fig. 2.—Microscopic section of liver of infant in case 1 showing giant multinucleated cells and increased connective tissue containing hemopoietic cells and inflammatory cells.

CASE 2.—The mother (same as in case 1) experienced a threatened abortion during the first trimester of her third pregnancy and was treated with large amounts of diethylstilbestrol. She was delivered uneventfully of a male infant on June 29, 1951, after 35 weeks' gestation. The child's birth weight was 4 lb. 8 oz. (2,041.17 gm.), and he measured 45 cm. (18 in.) in length.

7. Popper, H.; Steigmann, F., and Szanto, P. B.: Quantitative Correlation of Morphologic Liver Changes and Clinical Tests, Am. J. Clin. Path. **19**: 710, 1949.

His condition was described as fair at birth, but perioral cyanosis was noted. He was placed in an incubator with oxygen. Four hours after birth, the infant's condition had deteriorated and he was therefore seen by a pediatrician. Rales were found throughout both lungs, and considerable areas of atelectasis were noted. Oxygen and suction were used. The infant's condition became progressively worse, and he died six and one-half hours after birth. The important pathological findings at autopsy revealed a massive subarachnoid hemorrhage overlying the left cerebral hemisphere. There was no kernicterus. The lungs were airless. The liver was reddish and firm, with gross nodular formations noted. Microscopically, there was a striking alteration of the parenchyma basically similar to that described in detail in the protocol of case 1.

Comment

When the pediatrician was confronted with the hemorrhagic manifestations and downhill course of the infant in case 1, he could merely classify it as one of hemorrhagic disease of the newborn infant. The postmortem findings of severe liver damage seemed to implicate some toxic factor, the most obvious of which was the diethylstilbestrol that the mother had taken in large therapeutic doses during this and her prior pregnancies. A search of the literature, including many references to diethylstilbestrol toxicity in experimental animals, failed to reveal any evidence of severe fetal or maternal damage when the usual doses were employed.[8] Our large personal experience and that of many others does not include any toxic diethylstilbestrol effect.

TABLE 2.—*Blood Groups and Rh Types of Parents of Siblings, (Cases 1 and 2)*

	Blood Groups					Rh Type	Probable Genotype
		D	C	E	e		
Father	A	+	+	0	0	+	(R_1R_1) homozygous
Mother	A	+	0	+	+	+	(R_2r) heterozygous

A study was made of the literature on infantile and neonatal hepatitis [9] that appeared to be related to our two cases. We could reason that the mother of two infants might be a chronic carrier of the serum hepatitis form of viral hepatitis and had transmitted the virus to each fetus across the placenta. There is evidence cited in the literature indicating that this virus may remain active for many years in certain individuals,[10] as was demonstrated by transfer experiments in human volunteers. The carrier state may be associated with abnormal liver function tests in the mother [11] as well as in living siblings. The presence of abnormal liver function tests and an abnormal liver biopsy in our infants' mother appeared to favor a viral etiology. These findings perhaps could also be explained on the basis of an unusual sensitivity to diethylstilbestrol or to some unknown preexisting liver damage. Although the diagnosis of erythroblastosis was excluded by Dible in his own cases, and by others [12] because of the absence of demonstrable Rh or A-B-O blood group incompatibility or positive Coombs test, the resemblance of the pathology to that seen in certain instances of severe erythroblastosis has made us aware of the possibility of sensitization to some unknown or rare blood group in our cases. Antibodies could not be demonstrated in our two cases, although the parents' bloods were incompatible for **S, Kell, Le_a** and **P** blood factors. The mother's blood, however, was tested for antibodies nine months after delivery, so that if originally present they may have disappeared in the interval. It is possible for incompatibility to exist without a positive Coombs test.[13] Also in favor of erythroblastosis as the cause of this condition is the fact that none of the affected siblings was the firstborn. The presence of kernicterus in one of our cases is suggestive of a blood group incompatibility.

Conceivably, many cases of infantile and juvenile cirrhosis of the liver may be milder forms of the condition we have described, with lesser degrees of liver damage, compatible with survival to an older age. Other possible

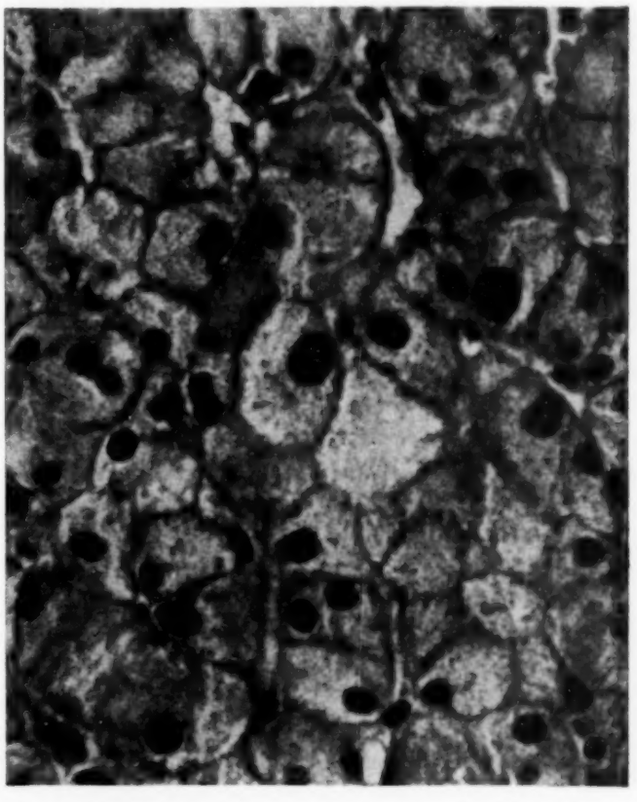

Fig. 3.—Microscopic section of mother's liver biopsy specimen (case 1) showing grade 1+ damage.

etiological factors to be considered are a genetic factor linked to blood groups causing an inherent liver defect and an inborn error of iron metabolism. There is no

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9. (*a*) Neefe, J. R., and others: Carriers of Hepatitis Virus in the Blood and Viral Hepatitis in Whole Blood Recipients: 1. Studies on Donors Suspected as Carriers of Hepatitis Virus and as Sources of Post-Transfusion Viral Hepatitis, J. A. M. A. **154**: 1066 (March 27) 1954. (*b*) Murray, R., and others: Carriers of Hepatitis Virus in the Blood and Viral Hepatitis in Whole Blood Recipients: 2. Confirmation of Carrier State by Transmission Experiments in Volunteers, ibid. **154**: 1072 (March 27) 1954. (*c*) Footnotes 2 and 1*c*. (*d*) Stokes, J. Jr.: Personal communication to the authors.

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specific prophylactic or active treatment for this disease in the present state of our knowledge. The accumulation of a larger body of case reports by other workers may help to clarify this syndrome.

Conclusions

In two cases of fatal hepatitis in newborn siblings the parents' bloods were free of demonstrable Rh or A-B-O incompatibility. The Coombs tests was negative. The disease is not sex linked. The infants survived but a few hours. Striking changes were found in the liver. There were coarse nodules and large multinucleated giant cells that contained great amounts of iron pigment. There was cirrhosis and excessive extramedullary hemopoiesis. The etiology is not clear. It may be viral, but a great weight of evidence points in the direction of incompatibility of some rare or unknown blood group. There is a resemblance to certain known cases of erythroblastosis with similar pathological features.

25 Central Park West (23) (Dr. Krainin).

PRACTICAL CONSIDERATIONS REGARDING TRACHEOTOMY

SURGICAL ERRORS AND SAFEGUARDS

Nicholas Georgiade, M.D., Carter Maguire, M.D., Hugh Crawford, M.D.
and
Kenneth Pickrell, M.D., Durham, N. C.

• Prophylactic tracheotomy is now justified in a wide variety of cases because of the continued improvement in techniques for doing the operation and caring for the patient. Especially in infants with respiratory difficulties, close observation permits tracheotomy to be done early, as elective surgery in the operating room, rather than as a late emergency procedure under adverse conditions.

A transverse skin incision prevents the later development of disfiguring scars. The exposure of the trachea must be done with certain precautions to avoid causing hemorrhage, spreading infection, or injuring the esophagus and laryngeal cartilages. The subsequent hygiene of the tracheostoma, the feeding of the patient, and the ultimate removal of the tracheotomy tube also demand special care.

Tracheotomy is not only necessary in certain types of respiratory obstruction or paralysis but is also lifesaving in cases of severe injury necessitating extensive surgery about the head, neck, or thorax.

Although the first tracheotomy is said to have been performed more than 2,000 years ago, only 25 successful tracheotomies were recorded until 1825.[1] Prior to 1800, the tracheotomy tube was short and straight. Shortly after the turn of the century, however, surgeons began to use both the curved and the double tube.[2]

The clinical aspects of a tracheotomy have now progressed to the point where this is no longer to be considered an emergency procedure but is preferably to be used prophylactically in a wide variety of cases. It is now considered good surgical judgment to perform a tracheotomy on patients with severe head and neck injuries (fig. 1) who are in danger of partial respiratory obstruction from their pharyngeal and tracheal secretions.[3] Patients with crushing injuries to the chest, patients in whom extensive thoracoplasties have been done, or patients with damage to the respiratory musculature, as in poliomyelitis, will be benefited by tracheotomy. A tracheotomy in these patients will reduce the physiological dead space and will make the tracheobronchial secretions more readily available for aspiration.[4] A prophylatic tracheotomy should be done in cases of extensive head and neck surgery involving radical neck dissections with resections of the tongue and mandible.[5] We have been including a tracheotomy as part of the above-mentioned procedures and also in bilateral radical neck dissections for the past 10 years.

From the Division of Plastic and Maxillofacial Surgery, Duke University School of Medicine and Duke Hospital.

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Indications for a tracheotomy in an infant are the same as for older children (fig. 2). There is, however, a significantly smaller margin of safety during the observation period prior to performing a tracheotomy. During this period of observation, the infant should be maintained in an atmosphere that is highly humidified and oxygenated.[6] The characteristic sign of nearly all types of laryngeal obstruction is inspiratory stridor.[7] In the infant, there is noticed a progressive restlessness accompanying the stridor. Air hunger, as well as sternal and intercostal retractions, is common in all patients with respiratory obstruction.

Types of Tracheotomies

Emergency Tracheotomy.—Emergency tracheotomy is a procedure of necessity, as the term implies. It is performed by placing a pillow or pad under the patient's

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shoulders so that the head will be hyperextended. After this, the thumb, second, and third fingers are arched over the trachea, inferior to the thyroid and cricoid cartilages, pushing the great vessels back under the sternocleidomastoid muscles. A transverse incision is then made down to the trachea. The third and fourth tracheal rings are incised in a vertical direction, and the tracheotomy tube is inserted.[8] In extreme emergencies, the use of a 14-16 gauge needle inserted into the cricothyroid space may be used effectively to maintain an airway until a lower tracheotomy can be performed. This area is preferred because of its stability and ease of localization, particularly in children. Hospitalized patients seldom need an emergency tracheotomy, as it is preferable to insert a laryngoscope and intubate the patient, which may temporarily relieve the respiratory obstruction. Later, if necessary, a tracheotomy can be performed in the operating room as an elective operation.

Fig. 1.—*A*, extensive bony and soft tissue damage to the maxillofacial region in patient in whom prophylactic transverse tracheotomy was performed. *B*, 16-year-old girl in whom a prophylactic longitudinal tracheotomy incision was done for a gunshot wound involving the mandible and soft tissues of the floor of mouth and neck. *C*, same patient three months after tracheotomy, with scar more prominent than the scar of original injury.

Fig. 2.—*A*, 6-week-old infant with a large cystic hygroma. *B*, prophylactic transverse tracheotomy performed as part of the operative procedure. *C*, 10 days after operation, patient with minimal post-tracheotomy deformity.

Prophylactic Tracheotomy.—Prophylactic tracheotomy is performed in the operating room. The patient's head is hyperextended. A local anesthetic agent may be used. A transverse incision is made two fingerbreadths (approximately 3 cm.) above the sternal notch (fig. 3*A*). The length of the incision is generally 3 cm., depending on the relative size of the patient. The underlying sternohyoid and sternothyroid muscles are retracted laterally (fig. 3*B*). The bleeding points may be either ligated or cauterized with the electrosurgical unit. The third and fourth cartilaginous rings are located. Two tracheal hooks are inserted laterally to stabilize the trachea. A vertical incision is then made through the midline cartilaginous area in the region of the fourth cartilaginous ring. The vertical incision is then extended into a "T" by means of a small transverse incision superiorly. The edges of the cartilage will roll out because of the traction from the tracheal hooks. A no. 5 tracheotomy tube can usually be inserted without difficulty in an adult (fig. 3*C*). A smaller one can be inserted depending on the size of the patient's trachea. An umbilical tape is tied around the back of the neck to hold the tube in position. One or two sutures of silk may be used to approximate the skin edges around the incision. A dry dressing is then placed around the tracheotomy tube.

Complications

Hemorrhage may occur from an inferior thyroid vein or from an anomalous artery, the thyroid ima artery, which commonly arises from the innominate artery and ascends in front of the trachea (fig. 3*B*). The isthmus of the thyroid may also be a source of hemorrhage. Wound infection is uncommon, even though emergency tracheotomies are performed frequently under nonsterile conditions. Some degree of subcutaneous emphysema may follow a tracheotomy. While this is usually limited to the cervical area, it may extend to the axillas and mediastinum, with a resulting pneumothorax. This complication can be decreased if there is minimal dissection of the adjacent cervical tissues and the wound incisions are not sutured too tightly.[9]

Injuries to the cricoid or thyroid cartilage areas, particularly during an emergency tracheotomy (that is made too high), will often result in laryngeal stenosis. The tube should be removed within the first day or a new lower tracheotomy site should be utilized to prevent any perichondritis or narrowing of the larynx. Infants and children have a mobile trachea that will "accordion" itself together during coughing. This can diminish the diameter of the trachea by up to one-half. If extreme care is not taken, the point of the scalpel may penetrate the anterior esophageal wall (fig. 3*D*). A fatal outcome may result from the leakage of ingested material into the trachea and eventual aspiration into the lungs.[10] In ap-

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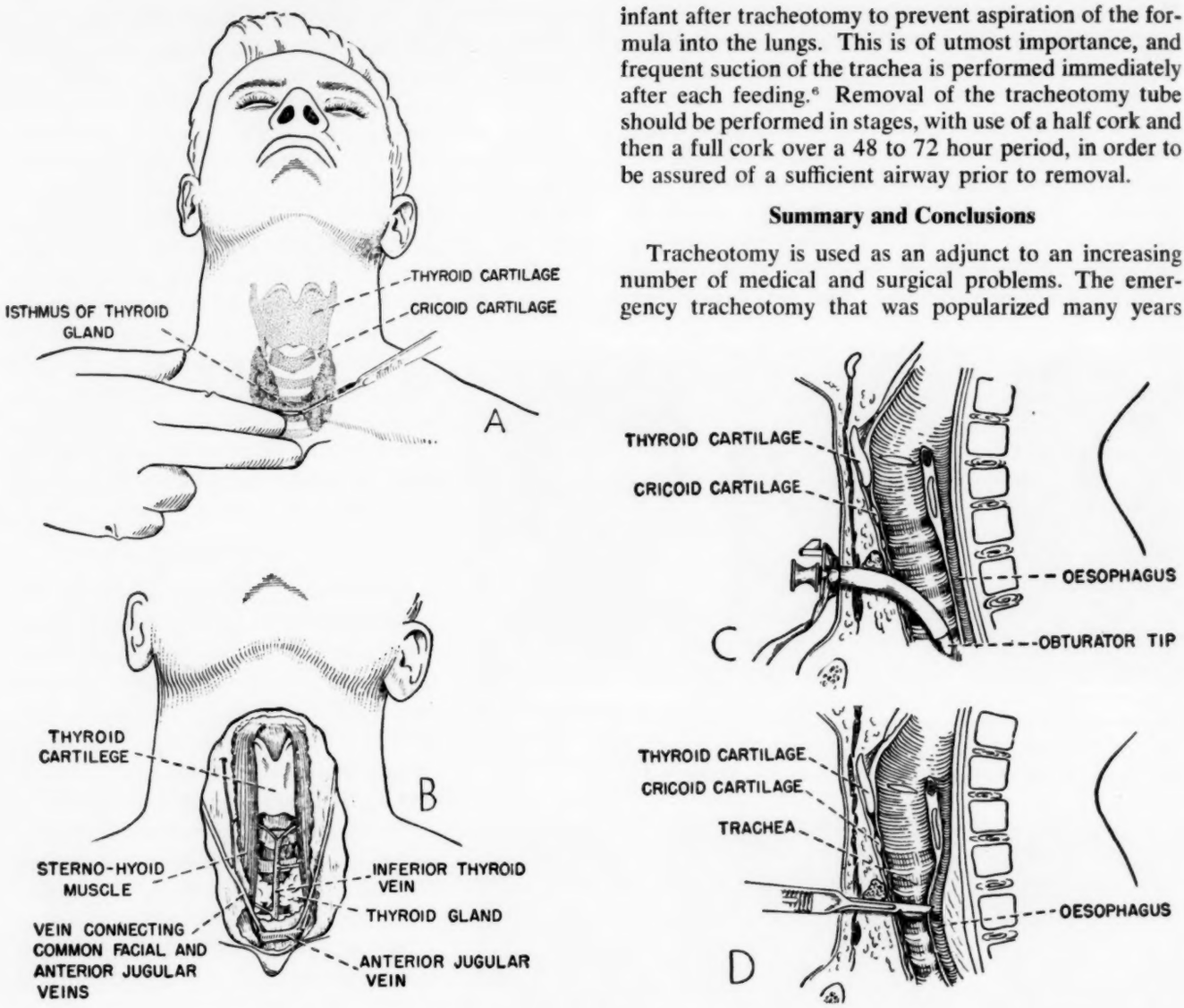

Fig. 3.—*A*, the supraclavicular tracheotomy site can be easily determined as the average width of two fingers. A transverse incision is then performed in the midline. *B*, some large veins and arteries are almost always present at the site of the tracheotomy. Troublesome bleeding can be prevented by prophylactic use of electrocoagulation. *C*, the tracheotomy tube should be properly inserted and positioned to prevent undue pressure on the posterior tracheal wall. *D*, an occasional complication of tracheotomies in infants and children. Care must be taken to maintain the patient as quiet as possible during the actual incision into the trachea. This will minimize the possibility of penetration into the esophagus as illustrated.

proximately 10% of the patients, encrustations will form. Some may attain a size sufficient to impair the airway. The period of greatest danger is from the 3rd to the 10th day. Purulent postnasal drip into the trachea, trauma to the trachea, or low humidity are predisposing factors.[11]

Post-Tracheotomy Care

It is most desirable to maintain a humid atmosphere to minimize the tracheal and alveolar irritation because of dehydration of the tissues. A humidifier should be utilized in the patient's room. All infants after tracheotomy should be placed in an Isolette oxygen tent, Croupette, or comparable type of plastic compartment, which is the most reliable means of regulating temperature, humidity, and oxygen concentration. In adults, a single moistened layer of gauze may be placed over the tracheotomy tube if the humidifier is not available.

Suction via the tracheotomy tube is performed frequently, and the inner tube is cleaned and changed several times daily. Particular care must be exercised in the infant after tracheotomy to prevent aspiration of the formula into the lungs. This is of utmost importance, and frequent suction of the trachea is performed immediately after each feeding.[6] Removal of the tracheotomy tube should be performed in stages, with use of a half cork and then a full cork over a 48 to 72 hour period, in order to be assured of a sufficient airway prior to removal.

Summary and Conclusions

Tracheotomy is used as an adjunct to an increasing number of medical and surgical problems. The emergency tracheotomy that was popularized many years ago has now given way to the performance of an elective tracheotomy, which is performed in the operating room. The use of a horizontal tracheotomy incision will prevent many postoperative disfiguring scars necessitating future plastic surgery.

11. Conley, J. J.: Diagnosis and Treatment of Encrustations in the Trachea, J. A. M. A. **154**: 829 (March 6) 1954.

Importance of Aldosterone.—Increased adrenal production of aldosterone is involved in the pathogenesis of a number of very common clinical disorders. That many more diseases will be found to be associated with increased or decreased secretion of this hormone seems abundantly clear. This prediction is based not only upon the numerous possibilities which exist but also upon the fact that clinical investigators have merely scratched the surface of this fertile field since the hormone was proved to exist and shown to be measurable. A still existent deterrent to rapid progress consists of the very difficult and laborious biological and biochemical procedures which are involved in such studies.—J. W. Conn, M.D., Aldosterone in Clinical Medicine—Past, Present, and Future, *A. M. A. Archives of Internal Medicine*, February, 1956.

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EFFECT OF UREA ON CEREBROSPINAL FLUID PRESSURE IN HUMAN SUBJECTS

PRELIMINARY REPORT

Manucher Javid, M.D.
and
Paul Settlage, M.D., Ph.D., Madison, Wis.

• Urea in amounts as high as 1 gm. per kilogram of body weight can be injected intravenously in the form of sterile, fresh 30% solution in 5% dextrose. Urea was used without causing toxic reactions in 21 patients. The desired reduction in cerebrospinal fluid pressure was accomplished in every case. There was no secondary rise such as is seen after injections of hypertonic solutions of sodium chloride and dextrose, and the blood pressure was unaffected.

Heat must not be used to sterilize the urea solution. If the technique is carefully followed, it should be valuable in brain surgery for the reduction of intracranial pressure.

The purpose of this report is to describe findings in a preliminary study to determine the safety and efficiency with which urea might be used intravenously for the purpose of reducing intracranial pressure. Many agents, including sodium chloride, sodium sulfate, sodium bicarbonate, magnesium sulfate, sodium arabinate, sorbitol, sucrose, and dextrose have been used in hypertonic solution for this purpose since the original work of Weed and McKibben in 1919.[1] All of these drugs are effective in reducing intracranial tension, but each has some undesirable action that limits or prohibits its use. Sodium chloride, for example, has a pronounced hypotensive effect, but the initial pressure reduction is followed by a secondary rise to pressure levels that exceed the original. The secondary rise may aggravate the patient's condition and has been held accountable as a cause of death.[2] Hypertonic sodium chloride is therefore no longer used. A degree of secondary rise in pressure has been demonstrated to occur after the administration of 50% dextrose, an agent that is frequently used today. Fifty per cent sucrose, although it produces little or no secondary rise, injures the renal tubules.[3] Evidence has been adduced by Lindberg [4] that the tubular damage is reversible and does not necessarily result in impairment of kidney function. However, this same author cautions against its indiscriminate use. In a publication of one of the commercial firms that prepares hypertonic sugar solutions for intravenous use, there is this comment: "Sucrose and dextrose have been shown to produce temporary hydropic degeneration of the renal tubular epithelium unaccompanied by detectable alteration in kidney function. Even though no clinically demonstrable harm has resulted, injections should probably not be repeated more frequently than at intervals of several weeks." [5]

That urea might be a promising hypertonic agent was suggested by the work of Fremont-Smith and Forbes in 1927 [6] and of Wolff and Forbes in 1928.[7] In the first of these two studies, marked cerebrospinal fluid pressure reductions were observed in three cats after intraperitoneal injection of 50% urea, and it was suggested, on the basis of this finding, that urea might prove to be useful clinically. In the 1928 study urea was administered intravenously to one cat, and again marked pressure reduction occurred.

In 1950, Smythe, Smythe, and Settlage [8] reported on the effects of intravenously given urea in monkeys. It was found that 17% urea, which has the same molecular concentration as 50% dextrose and twice the concentration of 50% sucrose, produces more pronounced and more persistent pressure drops than either of these sugars. When injections of 5 cc. per kilogram of body weight of 50% solutions of each of the three agents were compared for effect, it was found that the average pressure drop produced by urea was 4.5 times greater than that caused by sucrose or dextrose. It was also found, when the 5 cc. per kilogram dosages were compared, that the urea effects were much longer lasting. Pressures returned to normal in about 90 minutes with sucrose and dextrose, whereas pressures lower than the maximum drop produced by either of the sugars were present for a much longer period of time with urea.

Apparently the suggestion of Fremont-Smith and Forbes, that urea might be useful clinically for the purpose of reducing cerebrospinal fluid pressure, was never followed. As a matter of fact, we are not aware of any work, from the laboratory or clinic, other than that already mentioned. Urea has, however, been used clinically for other purposes than reduction of intracranial tension. It has long been recognized to be an effective diuretic agent. Salter states: "One of the most effective

From the departments of neurosurgery and anatomy, University of Wisconsin Medical School.

Prof. Frank L. Kozelka made the urea nitrogen determinations.

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1. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebro-Spinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**: 512-530 (May) 1919.

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3. Anderson, W. A. D., and Bethea, W. R., Jr.: Renal Lesions Following Administration of Hypertonic Solutions of Sucrose: Report of 6 Cases, J. A. M. A. **114**: 1983-1987 (May 18) 1940.

4. Lindberg, H. A.; Wald, M. H., and Barker, M. H.: Renal Changes Following Administration of Hypertonic Solutions (50 Per Cent Sucrose, 50 Per Cent D-Sorbitol, 50 Per Cent Dextrose and 10 Per Cent Sodium Chloride), Arch. Int. Med. **63**: 907-918 (May) 1939.

5. De Re Medica, Indianapolis, Eli Lilly & Company, 1951, p. 353.

6. Fremont-Smith, F., and Forbes, H. S.: Intra-Ocular and Intracranial Pressure: Experimental Study, Arch. Neurol. & Psychiat. **18**: 550-564 (Oct.) 1927.

7. Wolff, H. G., and Forbes, H. S.: Cerebral Circulation: IV. Action of Hypertonic Solutions, Arch. Neurol. & Psychiat. **20**: 73-83 (July) 1928.

8. Smythe, L.; Smythe, G., and Settlage, P.: The Effect of Intravenous Urea on Cerebrospinal Fluid Pressure in Monkeys, J. Neuropath. & Exper. Neurol. **9**: 438-442 (Oct.) 1950.

diuretic agents is urea, nature's own non-electrolytic diuretic." [9] For the purpose of promoting diuresis it is administered by the oral route, 20 gm. two to five times daily.[10]

LaLonde and Gardner [11] gave urea in conjunction with sulfonamides in the treatment of meningitis. These authors administered as much as 180 gm. daily for 15 days, and their findings indicate that it enhanced the effectiveness of the sulfonamides. The mild bactericidal action of urea, its inhibition of antisulfonamide substances, its proteolytic action, and its property of increasing the solubility of the sulfonamides were listed as possible factors contributing to the results that were obtained. Relief of intracranial tension was not listed as one of the therapeutic actions of urea. The findings of the present study suggest that this effect may also have been a factor influencing their results.

Vesell and co-workers [12] report the successful treatment of one case of subacute bacterial endocarditis in which the use of urea in combination with sulfadiazine was adopted for reasons similar to those listed by LaLonde and Gardner. The urea was administered intravenously in a concentration of 2%. Another of the few instances in which urea has been given by the intravenous route is found in the study of Steffensen.[13] He administered 30% solutions (usually 50 cc.) to 24 individuals for the purpose of determining total body water. It is thus evident that the clinical use of urea is not without precedent. It is a normal body metabolite that is well tolerated in large doses. This consideration, plus the experimental finding of its remarkable effectiveness as a hypertonic solution in monkeys, provided impetus for the present study.

Method and Procedure

Preparation of Urea Solutions.—Urea solutions may not be sterilized by boiling or autoclaving, since heat causes decomposition with liberation of ammonia. The 30% solutions used in this study were prepared by adding cool (room temperature) solution of 5% dextrose for intravenous use to sterile crystals. Vials containing the crystals were prepared in the department of pharmacy, University of Wisconsin, through the courtesy of Dr. Louis Busse and associates. With the use of aseptic technique, urea crystals were loaded into the rubber-stoppered vials under ultraviolet light.[14] The crystals, reagent quality, had been sterilized by washing in ether.

The choice of a 30% concentration of urea, with 5% dextrose rather than water as a solvent, was based on observations regarding the hemolytic effect of intravenously given urea in animals. It had been observed that aqueous solutions of urea, of varying concentrations, produced transient though quite marked hemoglobinuria. In vitro studies carried out by Roberts,[15] with both monkey blood and human blood, revealed that aqueous solutions of urea produced prompt hemolysis in both dilute and concentrated solutions. However, when urea was dissolved in either 5% dextrose or in isotonic sodium chloride solution, hemolysis did not occur within two hours when solutions were more dilute than 25%, whereas the higher concentrations did break down the red blood cells in this length of time. It was then shown that 30% solutions of urea, in either dextrose or saline solution, did not produce hemoglobinuria when injected in animals, while 50% solutions in these same solvents resulted in the output of urine that was cherry red in color. Accordingly, the 30% urea in 5% dextrose was adopted for this study.

Subjects.—In the early phases of the study, small doses of urea were administered to patients whose condition was hopeless. As the study progressed, larger amounts were administered, and, as observations bore out the expectation that urea would be well tolerated, some cases with better prognosis were included. The patients, 11 females and 10 males, thus constituted a heterogeneous group, ranging in age from 6 weeks to 59 years. The pathological diagnoses were as follows: intracranial neoplasm 13, including glioblastoma multiforme 6, metastatic carcinoma 2, angiosarcoma one, ependymoma one, astrocytoma one, cholesteatoma one, and meningioma one; brain abscess one; chronic subdural hematoma one; hypertensive encephalopathy one; cerebrovascular accident (hemorrhage) one; cerebral atrophy (arteriosclerosis) one; prefrontal lobotomy (for intractable pain) one; and congenital hydrocephalus 2. There were 24 intravenous injections in these 21 cases, three patients receiving two injections each. In addition to receiving two intravenous injections of urea, one of these last three patients also received sucrose intravenously and urea by gastric tube. Rectal administration of urea was also attempted in this same patient. Of the 24 intravenous injections of urea, 7 were made in the patients who had not undergone surgery, 3 were given at the time of craniotomy, 9 were at intervals from 12 hours to 11 days after craniotomy, and the remaining 5 injections were in cases where craniotomy had been carried out from one to five months previously.

Measurement and Recording of Cerebrospinal Fluid Pressure.—The Sanborn Polyviso with strain gauge was used to record pressure in one case. The method proved to be unsuitable for the long periods of observation required in this study, and therefore the standard open-end water manometer was used in all the other cases. The manometer, clamped to an ordinary ring-stand, was placed on a bedside table of appropriate height and connected to the puncture needle by a polyethylene tube.

Cerebrospinal fluid pressure was measured through a lumbar puncture needle in the majority of cases. It was measured through a ventricular needle in four instances,

9. Salter, W. T.: A Textbook of Pharmacology: Principles and Application of Pharmacology to the Practice of Medicine, Philadelphia, W. B. Saunders Company, 1952.

10. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students, New York, the Macmillan Company, 1941.

11. LaLonde, A. A., and Gardner, W. J.: Effect of Urea on Bactericidal Action of Sulfonamide Drugs: Report of 5 Cases of Bacterial Meningitis, J. A. M. A. **138**: 406-408 (Oct. 9) 1948.

12. Vesell, H.; Gross, I. H., and Sussman, R. M.: Urea as an Adjunct to Sulfonamide Therapy: Report of Its Successful Use in a Case of Subacute Bacterial Endocarditis, J. Lab. & Clin. Med. **31**: 444-452 (April) 1946.

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14. Parrott, E. L.; Wurster, D. E., and Busse, L. W.: The Preparation of Sterile Ophthalmic Solutions, J. Am. Pharm. A. (Pract. Pharm. Ed.) **14**: 645-647 (Oct.) 1953.

15. Roberts, T. R.: Urea as an Agent for the Reduction of Intracranial Pressure, unpublished medical thesis studies, University of Wisconsin, 1955.

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and lumbar and ventricular pressures were measured simultaneously in one case. In one patient (one of the three who received urea in the operating room at the time of craniotomy) pressure was not measured; in this case observations were limited to the attempt to note changes in brain bulk after the dura had been exposed.

Patients were always in the lateral decubitus position for pressure observations. Except in a few cases where the urgency of circumstances did not permit, control pressure readings were obtained for a period of 30 to 60 minutes prior to urea injection. When pressure changes were occurring rapidly, as after injection of urea, readings were recorded once every minute. At other times they were recorded at five minute intervals. Pressure changes were followed as long as the condition in each case permitted. This was usually for a period of four to six hours. The length of the observation periods ranged from an interval of less than one hour to periods as long as 17 hours. Small doses of sedatives were administered when there was unusual restlessness or discomfort. Only the three patients studied at the time of craniotomy were under general anesthesia.

Blood and Spinal Fluid Urea Determinations.—A preliminary survey of the course of changes in blood and spinal fluid urea levels after injection was included in this study. For this purpose, blood samples were obtained before and at varying intervals after injection in the majority of cases. Spinal fluid samples were taken when pressure measurements were discontinued, and in some cases blood and spinal fluid were obtained at intervals of one or more days after injection. Urea nitrogen content was determined by the Archibald colorimetric method.[16]

Results

Table 1 has been prepared to show the decrease in pressure produced by intravenously given urea. It shows that there was a fall in pressure in each instance, even when so small an amount as 100 mg. per kilogram of body weight was administered. However, it is evident that there was no correlation between the absolute degree of change in intracranial tension and the amount of urea administered. It is apparent from the table that the initial pressure level was one of the factors that influenced the result. The highest pressure observed, for example, was in case 10, and it was in this case also that the greatest absolute change was noted, even though only 200 mg. per kilogram was administered. The physiological condition of the patients was undoubtedly another factor that must be considered in evaluating the findings. The patient in case 21, for example, received urea as an emergency measure when she was in a critical condition. The 800 mg. per kilogram improved her condition somewhat, but in a matter of hours her status had so deteriorated that she was dying, and an additional 1,000 mg. per kilogram was administered. The relatively small pressure changes in this case must be assessed in terms of the patient's terminal condition and the low initial pressure levels.

TABLE 1.—*Maximum Reductions in Cerebrospinal Fluid Pressure After Administration of Urea*

Case No.	Sex	Age, Yr.	Diagnosis *	Status Regarding Surgery	Urea, Mg./Kg.	Initial Pressure, Mm.	Pressure Decrease, Mm.	Decrease, %
1	M	56	Glioblastoma multiforme	3 days postoperative	100	460	210	45
2	M	46	Angiosarcoma	6 days postoperative	100	161	44	27
3	F	53	Cerebral atrophy (arteriosclerosis)	No surgery	100	197	57	28
4	F	42	Hypertensive encephalopathy	No surgery	100	384	210	54
5	F	6 wk.	Congenital hydrocephalus	No surgery	100	147	34	23
6	F	59	Prefrontal lobotomy for pain	38 days postoperative	100	...	...	..
7	F	2 mo.	Congenital hydrocephalus	No surgery	200	276	144	52
8	F	46	Metastatic carcinoma	No surgery	200	106	46	43
9	F	54	Glioblastoma multiforme	Preoperative	200	183	83	45
10	M	31	Chronic subdural hematoma	General anesthesia	200	850	574	67
11	M	47	Glioblastoma multiforme	3 days postoperative	300	239	209	87
12	M	29	Cholesteatoma	General anesthesia	300	462	192	41
13	M	58	Glioblastoma multiforme	2 days postoperative	400	600	275	45
14	M	43	Glioblastoma multiforme	10 wk. postoperative	400	500	390	78
15	M	58	Metastatic carcinoma	No surgery	400	385	285	74
16	M	51	Glioblastoma multiforme	16 wk. postoperative	500	331	230	69
17	M	29	Cholesteatoma	11 days postoperative	500	392	158	40
18	F	35	Meningioma	8 wk. postoperative	600	136	110	87
			100 cc. 50% sucrose	15 wk. postoperative	...	137	66	48
			Slow I.V. drip	16 wk. postoperative	600	146	166	113
			Gastric tube	19 wk. postoperative	600	136	111	81
19	F	7	Cerebellar astrocytoma	10 days postoperative	600	216	147	68
20	F	53	Cerebrovascular accident (hemorrhage)	1 day postoperative	700	274	255	93
21	F	7	Ependymoma, 4th ventricle	1 day postoperative	800	130	94	72
22	M	18	Multiple brain abscesses	During surgery	900	...	...	..
23	F	7	Ependymoma, 4th ventricle	2 days postoperative	1,000	85	65	76

* Unless otherwise noted lesions are supratentorial.

The table lists all of the cases included in the present study. Urea was administered by rapid intravenous injection (average rate of 20 cc. per minute) 22 times, it was given twice by slow intravenous injection and by gastric tube on one occasion. Sucrose was used for comparison with urea in case 18. No pressure measurements were obtained in case 22, in which observations were limited to the attempt to note brain shrinkage by direct observation at the time of surgery; pressure findings are not given in case 6, since mechanical recording used in this case did not prove to be satisfactory. The initial pressures listed were obtained by averaging the readings for the last 15 to 20 minutes of the control period, and the amount of pressure decrease was cal-

16. Archibald, R. M.: Colorimetric Determination of Urea, J. Biol. Chem. **157**: 507-518 (Feb.) 1945.

culated by subtracting the lowest reading obtained, following the injection, from the initial pressure. The significance of the pressure values obtained must be interpreted in terms of the condition of the patient.

The curves that have been prepared (fig. 1, 2, and 3) illustrate the time course of the pressure changes that have been observed. The figures include an example of each of the dosages that has been used, with the exception of the 800 and 1,000 mg. per kilogram doses that were administered to the patient in case 21 and the 900 mg. per kilogram dose received by the patient in case 22. In this last case there was only direct observation of the effect of urea on brain bulk. Pressure was not measured.

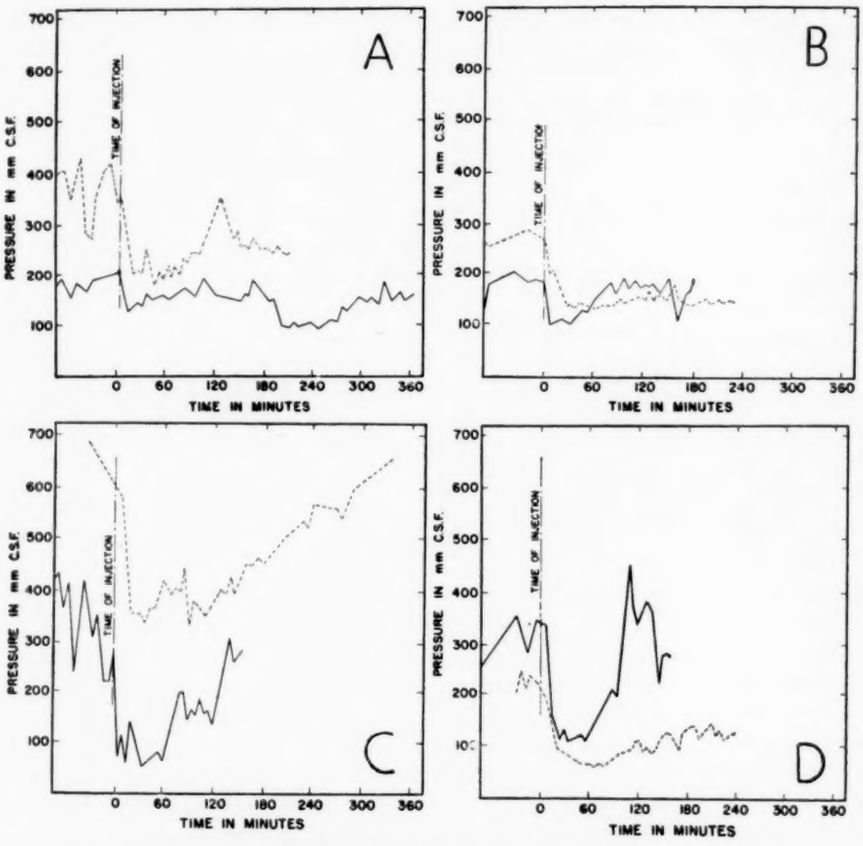

Fig. 1.—Effect of intravenously given urea on cerebrospinal fluid pressure in eight cases. *A*, effect in two patients who received 100 mg. per kilogram of body weight. Broken line, case 4. Patient was an obese woman with hypertensive encephalopathy. Pressure rise two hours after injection was due to restlessness. Solid line, case 3. No explanation for secondary fall in pressure three hours after injection in this patient with cerebral atrophy secondary to arteriosclerosis. *B*, effect in two patients who received 200 mg. Broken line, patient with congenital hydrocephalus and ventricular pressure (case 7); solid line, patient with preoperative glioblastoma (case 9). Both patients showed a definite and prompt fall in pressure. Relatively rapid return of pressure toward preinjection levels, as seen in case 9, appears characteristic of patients with rapidly expanding intracranial lesions. *C*, effect in two patients (broken line, case 13; solid line, case 11) who received 400 and 300 mg., respectively, two and three days after operation. Patient in case 13 had glioblastoma multiforme; patient in case 11 glioblastoma multiforme and ventricular pressure. *D*, effect in two patients (broken line, case 19; solid line, case 16) who received 600 and 500 mg. respectively. Patient in case 16 had undergone right occipital craniotomy for glioblastoma multiforme four months prior to urea study. Patient in case 19 had undergone suboccipital craniectomy for removal of a midline cerebellar astrocytoma 10 days previously.

Opportunity for direct observation of the brain following injection was afforded in three cases. In two of these (cases 10 and 12) urea had been injected and pressure reduced before the craniotomy opening was complete. Though the initial pressure was high in both cases (850 and 462 mm. respectively) the dura was not tense when the bone flap was turned down. In the third case, urea was not injected until the dura was exposed. It was found to be under marked pressure. A small dural incision, 2 to 3 mm. in length, demonstrated the tendency of the brain to herniate. When urea was first injected there was a palpable decrease in the tension of the dura and the brain. Tendency to herniate did, however, continue to exist in this case of brain abscess. It was felt that the relatively slight response to urea in this patient reflected a state of peripheral vascular collapse. Cheyne-Stokes respiration was present prior to injection of urea, and the initial development of the metastatic brain abscess was related to the presence of a severe congenital cardiac anomaly.

The pressure findings in two of the cases provide indirect evidence of the capacity of urea to reduce brain bulk. The findings in case 13 (fig. 1*C*) were interpreted as suggesting that reduction in brain bulk led to the removal of a block in the cerebrospinal fluid pathway. The findings in a second patient (second injection, case 17) lend themselves to a similar interpretation. Eleven days after the removal of a large cholesteatoma the condition of this patient suddenly deteriorated. It seemed likely that this change was due to herniation of the uncus through the tentorial notch. Five hours after this sudden change in the patient's condition, urea, 500 mg. per kilogram, was injected. Forty-five minutes after injection the pressure had decreased from an initial level of 400 mm. to 130 mm. At this juncture the lumbar pressure began to rise and in a matter of 10 seconds had risen to exceed the 600 mm. mark. There was no overt change in the patient's condition at the time of this sudden increase in lumbar spinal fluid pressure. The explanation of the precipitous rise in lumbar pressure seems to be that release of obstruction in the cerebrospinal fluid pathway allowed the fluid, under excessively high pressure in the cranial cavity, to rush into the spinal canal and to reflect this fact by the manometric change that was observed.

Report of Cases

CASE 18.—A 35-year-old woman was comatose for four months after the second of two craniotomies for olfactory groove meningioma at another hospital. Because of her immobility, and because her general condition had been stable for several months, it was possible to make accurate pressure measurements over long periods. The patient received identical amounts of urea (120 cc. of 30%—600 mg. per kilogram) on three occasions, and a fourth study was made with the administration of 100 cc. of 50% sucrose. The urea was administered by rapid intravenous injection (40 cc. per minute) for one study, by slow intravenous drip (3 cc. per minute) for another, and by gastric tube for the third study. The most marked effect, producing a negative pressure (20 mm. below the level of the lumbar needle) was obtained when urea was administered by slow drip. The other two methods of urea administration gave lesser effects

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and were approximately equivalent. One hundred cubic centimeters of 50% sucrose was given because it was considered a common dosage. It produced less effect than any of the urea administrations. As figure 2 illustrates, water was given at 9 and again at 11½ hours in the two longer studies. In all probability, this was responsible for the subsequent increase in rate of pressure rise.

CASE 20.—A comatose woman, aged 53, was admitted to the hospital with increased intracranial pressure due to intracerebral and subarachnoid hemorrhage. Exploratory right subtemporal craniotomy and decompression the day prior to urea studies had not improved her condition. During the urea study she was in the left lateral position and remained motionless throughout the 17 hour procedure. Urea, 700 mg. per kilogram given by slow intravenous drip over a period of 66 minutes, produced a 250 mm. decrease in pressure. As in the case of the two long studies in the patient in case 18 (fig. 2), the rate of pressure rise was increased toward the end of the study by fluid administration. Seven and a half hours after urea administration, labored respiration and gagging indicated that the patient was reacting to the pharyngeal airway that had been in place since surgery, which was performed the night before these studies were made. The prompt and sustained fall in pressure that occurred immediately on removal of the airway suggests that there is an element of artefact in the pressure levels that had been recorded during the preceding one to two hours (fig. 3).

The patient's urinary output for the 24 hour period preceding the conclusion of this study was 1,600 cc. The diuretic effect of urea is illustrated by the fact that a little more than half of this 24 hour output occurred during the 12 hours following injection of urea, during which time only 300 cc. of fluid (in addition to the 150 cc. of 30% urea) was administered. Blood

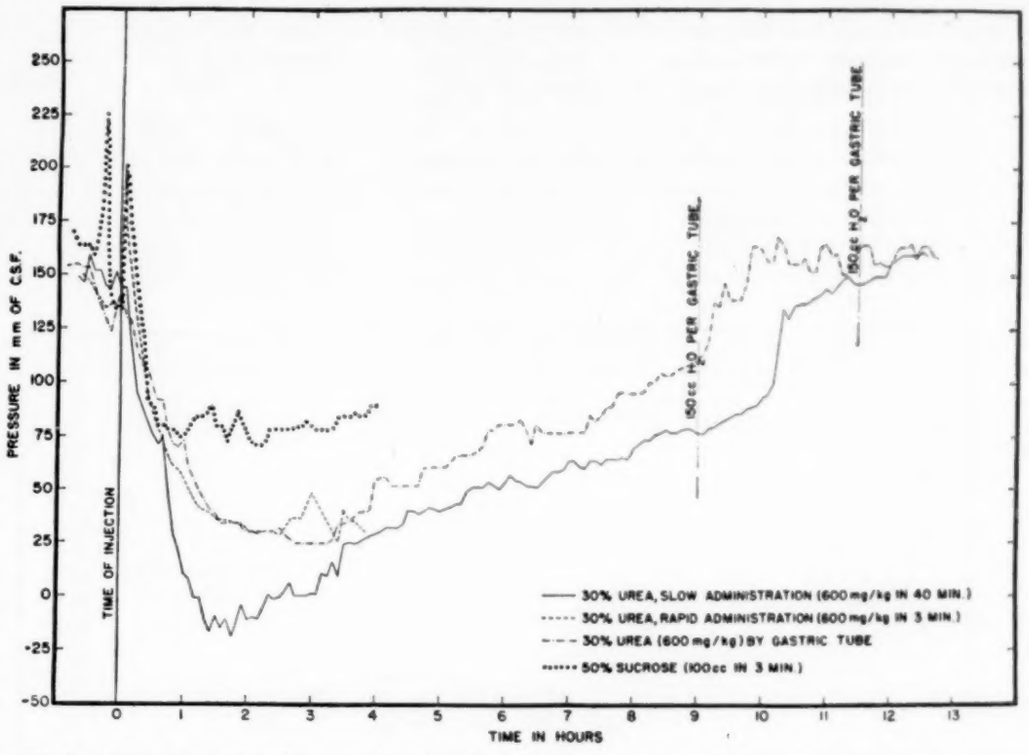
PRESSURE IN mm OF C.S.F.
TIME IN HOURS
TIME OF INJECTION
150cc H2O PER GASTRIC TUBE
150cc H2O PER GASTRIC TUBE
30% UREA, SLOW ADMINISTRATION (600 mg/kg IN 40 MIN.)
30% UREA, RAPID ADMINISTRATION (600 mg/kg IN 5 MIN.)
30% UREA (600 mg/kg) BY GASTRIC TUBE
50% SUCROSE (100cc IN 3 MIN.)

Fig. 2.—Effect of urea given intravenously and orally and of sucrose on cerebrospinal fluid pressure in patient (case 18) in whom two craniotomies had been done for olfactory groove meningioma.

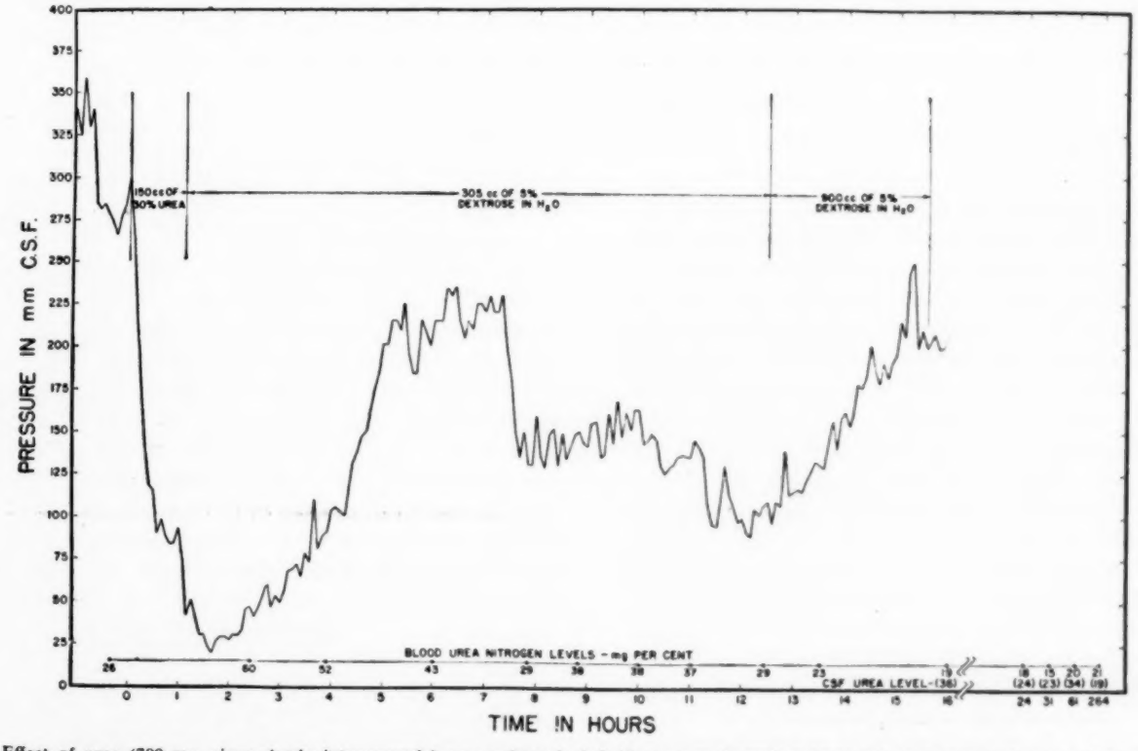
PRESSURE IN mm C.S.F.
150cc OF 30% UREA
305 cc OF 5% DEXTROSE IN H2O
900cc OF 5% DEXTROSE IN H2O
BLOOD UREA NITROGEN LEVELS - mg PER CENT
CSF UREA LEVEL-(38)
TIME IN HOURS

Fig. 3.—Effect of urea (700 mg. given slowly intravenously) on cerebrospinal fluid pressure in patient (case 20) in whom exploratory right subtemporal craniotomy and decompression had been done for intracranial pressure due to intracerebral and subarachnoid hemorrhage.

pressure was taken every 15 minutes throughout the period of this study, and no significant changes were observed. (Less systematic observation in other cases support this finding.)

Though all generalizations based on the results of this study must be considered as provisional in view of the small number of cases on which they are based, the findings as related to the effectiveness of urea as an agent for the reduction of intracranial tension may be summarized as follows: 1. In every dosage employed from 100 to 1,000 mg. per kilogram, 30% solution of urea produced a definite fall in pressure. 2. With high initial pressure, the hypotensive effects are relatively greater. 3. Urea produces an apparent shrinkage of brain volume. 4. In the presence of rapidly expanding lesions the pressure reduction is less well sustained than when the intracranial condition is quiescent. 5. In the one case in which comparisons were made, the best results were obtained by slow intravenous drip. The gastric tube and rapid intravenous methods of administration were somewhat less effective and approximately equivalent to each other. Urea was immediately expelled when given per rectum. 6. Urea injection has no significant effect on blood pressure. 7. Secondary rises in cerebrospinal fluid pressure, such as those which occur with the use of hypertonic saline solution and dextrose, did not occur following the injection of urea.

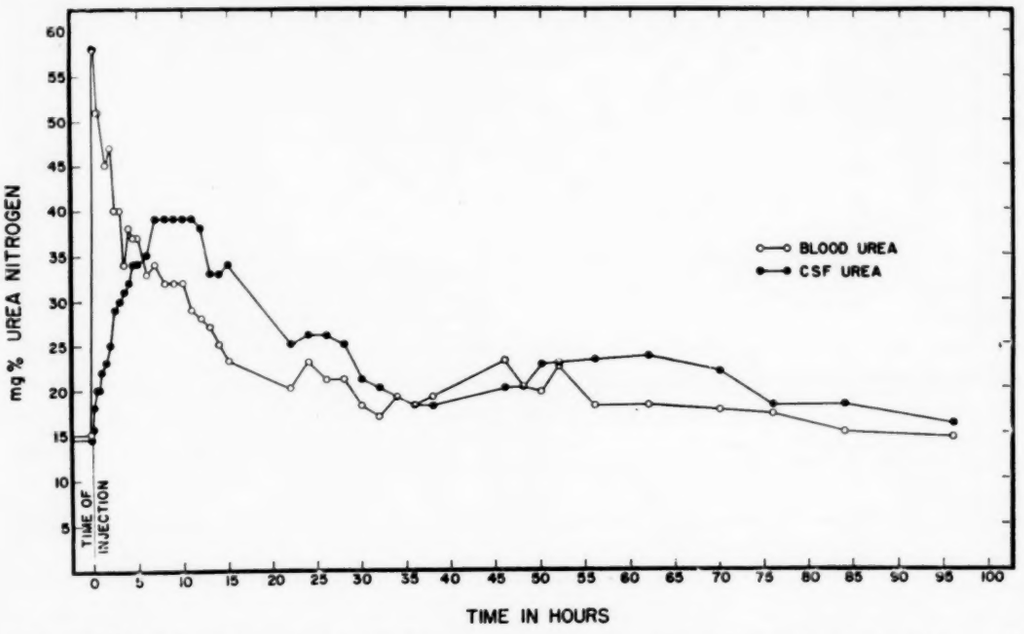

Fig. 4.—Blood and cerebrospinal fluid urea nitrogen levels after intravenous administration of urea (120 cc. of 30% urea in three minutes).

The blood urea levels, given in table 2, were unremarkable. As might have been expected, the highest levels were recorded soon after the administration of urea. Levels then declined, and the evidence that is available indicated that the blood clears to preinjection levels by about 12 hours after administration. It is interesting to note that there are several cases in which the cerebrospinal fluid urea level was found to be higher than the blood urea level after the blood levels had returned to normal (fig. 4). Whether this finding of a reversal in the normal relationships of blood and cerebrospinal fluid urea levels will be a consistent one remains to be determined. It appears, however, that this inverse relationship is similar to that which has been observed with other readily diffusible substances. Alcohol, for example, does not reach its maximum concentration in the cerebrospinal fluid until two hours after administration, but then there is a period during which cerebrospinal fluid alcohol concentration remains above the blood level.

Comment

Symptoms such as loss of appetite, nausea, vomiting, prostration, and apathy develop when urea blood levels become excessive. The magnitude of the blood levels at which these symptoms occur is variously given by different authors (Sollmann 70 mg.,[17] Salter 250-300 mg.[9]). Though the relatively mild toxic effects, such as anorexia, nausea, and apathy, could not have been observed in those of the patients in the present series who were critically ill or dying, no complaints were made by those of the patients who were oriented and cooperative. The absence of evidence of toxicity is consistent with blood urea nitrogen levels listed in table 2. The highest level recorded is 90 mg. per 100 cc. Though additional values equaling or somewhat exceeding this figure would undoubtedly have been obtained with earlier blood sampling in the cases in which the larger amounts of urea were injected, these peak values would obviously have been transient and near the lower limits of the toxic levels that have been listed.

Vesell and others,[12] stated that they used urea in concentrations of 2% because higher concentrations cause local venous thrombosis at the site of injection. No thrombosis was observed in the present series, with the use of 30% urea, but this may merely reflect differences in the duration and frequency of the periods of injection. Steffensen,[13] who used intravenously given 30% urea for determination of total body water, states that thrombosis occurred in several of the 24 individuals to whom he administered the drug. His statement, which bears on the matter of toxicity, is as follows: "The discomforts of the procedure [injection of 50 cc. of 30% solution of urea] have been rather moderate. In a few cases an aseptic thrombosis of a vein in the forearm has been observed after the injection and two of the experimental persons had a transient rise in temperature, but in both cases the solution used for the injection had been standing more than three weeks after the preparation."

17. Sollmann, T.: A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology, ed. 7, Philadelphia, W. B. Saunders Company, 1948.

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We wish to emphasize that the problem of possible toxic effects resulting from intravenous injection of urea merits further careful attention. Steffensen implicates "stale" solutions. It has been the experience of one of us (P. S.) that old solutions were lethal when they were given to a series of four cats. The solutions used in these four animals had been made up several months previously and had been kept in rubber-stoppered vials. At the time when the solutions were first prepared, they had been used in cats without evidence of ill-effects. It was because of this experience that only freshly prepared solutions were used in the present study. The question of whether truly sterile solutions may be preserved indefinitely without decomposition is being investigated at the present time.

It should be emphasized that urea solutions are not to be heated. As pointed out previously, heating produces decomposition with liberation of ammonia. Streicher [18] reported fatal results after the administration of urea in dogs. There may be a species factor in dogs that makes them intolerant to urea. However, since Streicher heated his solutions in order to administer them at body temperature, it is possible that they were overheated to the point of producing decomposition.

Though the tentative conclusion of this preliminary study is that intravenously given urea effectively reduces intracranial hypertension and that it may be administered safely in doses such as those that have been employed, the whole question as to its therapeutic efficacy remains unexplored. Symptoms of some of the patients in the present series were temporarily ameliorated, but there has been no attempt to assess the possibility that repeated administrations of urea might maintain a condition of improvement. Further work is necessary to determine the practical applications. Some of the questions that should be studied are: What is the optimal dose of urea, and at what rate and by what route shall it be administered? How often may the administration be repeated, and can satisfactory fluid balance be maintained in the face of the dehydration that is produced by urea? Will urea prove to be an agent superior to sucrose or dextrose in neurological and neurosurgical cases where hypertonic solutions are indicated? Will repeated administration of urea be beneficial in reducing the cerebral edema that follows intracranial surgery?

If further work demonstrates that urea may be administered repeatedly without producing toxic effects, it is possible that the range of indications for the use of hypertonic agents may be extended. Some of the conditions in which it may be worthwhile to investigate the effect of urea are hypertensive encephalopathy, lead encephalopathy, pseudotumor cerebri, Ménière's disease, meningitis, and encephalitis.

TABLE 2.—*Blood and Cerebrospinal Fluid* Urea Levels Before and at Intervals After Intravenous Injection of Urea*

Case No.	Amount Injected, Mg./Kg.	Before Injection, Mg./100 Cc.	After Mg./100 Cc.									
			5-10 Min.	11-20 Min.	21-30 Min.	31-60 Min.	1-2 Hr.	2-3 Hr.	3-4 Hr.	4-6 Hr.	12-24 Hr.	24-72 Hr.
1	100	14.0	....	....	....	27.5	....	27.0	....	....	13.5	....
3	100	31.0	34.0	....	....	....	....	....	....	27.0 (28.0)	....	....
4	100	10.0	....	31.0	....	....	....	....	22.5 (13.5)	....	15.0	....
5	100	20.8	....	....	....	....	....	....	27.5 (22.5)	....	....	....
6	100	21.5	40.5	....	....	....	27.0	....	....	....	23.0	....
7	200	15.0	....	....	....	....	....	....	....	23.5 (19.0)	....	13.5 (17.5)
8	200	9.0	....	....	....	....	....	14.0	....	....	7.0	....
9	200	9.0	....	....	....	....	....	19.5 (12.5)	....	....	....	....
10	200	21.0	....	....	....	....	31.0	....	....	....	18.5	....
11	300	17.0	....	....	....	....	....	33.5 (21.5)	....	....	21.5	....
14	400	8.0	....	....	....	....	....	....	30.0 (14.0)	....	....	13.0
15	400	13.0	....	....	....	....	....	40.0	39.0 (18.0)	....	16.0	....
16	500	21.0	....	....	52.0	....	47.0	45.0 (22.0)	....	....	....	15.0
17	500	10.8	....	....	....	44.2 (20.0)	38.5 (26.0)	....	....	....	22.8	....
18	600	7.0	....	86.0	....	....	....	....	51.0 (36.0)	....	5.2	....
19	600	26.0	....	....	....	....	....	90.0	....	55.0 (39.0)	39.0	23.0
20	700	26.0	....	....	....	....	....	60.0	52.0	43.0	19.0 (36.0)	15.0 (23.0)

* Cerebrospinal fluid urea levels are given in parentheses.

Though results were extremely variable, because of the wide variety of conditions and the near-terminal state of some of the subjects, decrease in cerebrospinal fluid pressure was observed in all cases with dosages ranging from 100 to 1,000 mg. per kilogram of body weight. Substantial and prolonged decrease in pressure was observed in some of the cases. A preliminary survey indicated that blood was cleared to preinjection levels of urea content in about 12 hours. It was found in several instances that the spinal fluid urea level was higher than blood urea level after blood levels had returned to normal. No toxic results were observed, but it was emphasized that problems of possible toxic effect warrant additional careful study. It is particularly important to guard against the use of impure or improperly prepared solutions of urea.

Summary

Thirty per cent solutions of urea in 5% dextrose were administered intravenously to 21 patients. In one case the results of various methods of administration—slow intravenous drip, rapid intravenous injection, and gastric tube—were compared. Sucrose was given intravenously to this same patient, and attempted rectal administration of urea was unsuccessful. Though results were extremely variable, because of the wide variety of conditions and the near-terminal state of some of the subjects, decrease in cerebrospinal fluid pressure was observed in all cases with dosages ranging from 100 to 1,000 mg. per kilogram of body weight. Substantial and prolonged decrease in pressure was observed in some of the cases. A preliminary survey indicated that blood was cleared to preinjection levels of urea content in about 12 hours. It was found in several instances that the spinal fluid urea level was higher than blood urea level after blood levels had returned to normal. No toxic results were observed, but it was emphasized that problems of possible toxic effect warrant additional careful study. It is particularly important to guard against the use of impure or improperly prepared solutions of urea.

1300 University Ave. (6) (Dr. Javid).

18. Streicher, M. H.: Experimental Uremia: Uremic Enteritis, Arch. Int. Med. **42**: 835-845 (Dec.) 1928.

VENTRICULAR SEPTAL DEFECTS WITH PULMONARY HYPERTENSION

SURGICAL TREATMENT BY MEANS OF A MECHANICAL PUMP-OXYGENATOR

James W. DuShane, M.D., John W. Kirklin, M.D., Robert T. Patrick, M.D.,
David E. Donald, B.V.S., M.R.C.V.S., Howard R. Terry Jr., M.D., Howard B. Burchell, M.D.
and
Earl H. Wood, M.D., Ph.D., Rochester, Minn.

• *Congenital ventricular septal defects have been corrected in a group of 20 patients by open cardiotomy with the help of a mechanical pump-oxygenator. Direct suture was done in 3; in the other 17 a nonabsorbable sponge was sutured into the opening. Extracorporeal circulation was maintained by cannulas diverting blood from the superior and inferior venae cavae to the pump and an additional cannula directing the blood from the pump into the aorta through the previously divided left subclavian artery.*

Four patients died during the postoperative period as a result of pulmonary complications. In most of the others the hypertension previously existing in the pulmonary system was substantially reduced, and in all there has been a pronounced improvement in general well-being. The preoperative heaving cardiac action has disappeared.

Selection of candidates for this operation depends on accurate physiological studies, including cardiac catheterization. It is believed that patients with significant symptoms from ventricular septal defects associated with left-to-right shunts should have the defects closed.

Open intra ardiac operations for the repair of ventricular septal defects have been performed on 20 patients at the Mayo Clinic. These patients are part of a group of 38 who had various types of congenital heart disease and on whom open cardiotomy had been accomplished at the clinic with the aid of a mechanical pump-oxygenator.[1] These operations were done between March and October, 1955, inclusive; the first four cases were mentioned in a previous publication.[2] In the only other completely reported series of cases of successfully treated ventricular septal defects repaired during open cardiotomy, the circulation of the patient was supported by means of a human donor.[3]

Clinical Features

A ventricular septal defect associated with pulmonary hypertension is a serious disorder that may result in death in early infancy,[4] a handicapping disability in childhood, or invalidism and a shortened life span in adults. All 20 of these patients had significant symptoms and cardiac enlargement, with moderate to severe degrees of pulmonary hypertension. Clinical features were similar in all, differing only in degree. These included a history of feeding difficulties during infancy, undernutrition, easy fatigability, and an apparent increase in susceptibility to pulmonary infections. The usual physical findings typical of ventricular septal defect with pulmonary hypertension were noted, including tumultuous cardiac action, a systolic thrill, and a long, harsh systolic murmur at the lower left sternal border, with accentuation of the second heart sound at the pulmonic valve area.

Of the 20 patients, 19 were children 12 years of age or less and one was a 29-year-old man. All but two of the children were underweight and were moderately to seriously handicapped with regard to exercise tolerance, while the adult was a semi-invalid. Cardiac enlargement was demonstrated in all 20 patients by radiological examination (fig. 1); in addition, increased pulmonary vascularity was a prominent feature. Data are summarized in table 1.

Laboratory Data.—All patients underwent preoperative cardiac catheterization, which disclosed the significant hemodynamic findings of substantial arteriovenous shunts, occasional small venous-arterial shunts, and pulmonary hypertension (table 2). The systolic blood pressure in the pulmonary artery was 80% or more of the peripheral systemic arterial pressure in 11 patients and between 60 and 79% in 4 patients (table 3). Since the peripheral systemic arterial pressure normally averages 15% higher than the aortic pressure, it is thought proper to consider the pressure in the pulmonary artery in these 15 patients to be approximately equivalent to that of the aorta.[5] The total pulmonary arterial resist-

TABLE 1.—*Clinical Data on Twenty Surgical Patients with Ventricular Septal Defect*

	No. of Patients
Weight	
15-50% below normal	17
Average	3
Enlarged heart, grade 1-4 (av. = grade 3)	20
Electrocardiogram	
Right ventricular hypertrophy	20
Left ventricular hypertrophy	18

From the Mayo Clinic and Mayo Foundation, sections of pediatrics (Dr. DuShane), surgery (Dr. Kirklin), anesthesiology (Drs. Patrick and Terry), medicine (Dr. Burchell), and physiology (Dr. Wood). Mr. Donald is a Research Associate.

The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

1. Jones, R. E., and others: Apparatus of the Gibbon Type for Mechanical Bypass of the Heart and Lungs: Preliminary Report, Proc. Staff Meet., Mayo Clin. **30**: 105-113 (March 23) 1955.

2. Kirklin, J. W., and others: Intracardiac Surgery with the Aid of a Mechanical Pump-Oxygenator System (Gibbon Type): Report of 8 Cases, Proc. Staff Meet. Mayo Clin. **30**: 201-206 (May 18) 1955.

3. Lillehei, C. W., and others: The Results of Direct Vision Closure of Ventricular Septal Defects in 8 Patients by Means of Controlled Cross Circulation, Surg. Gynec. & Obst. **101**: 447-466 (Oct.) 1955.

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ance, expressed in dynes seconds centimeter $^{-5}$, was extremely high in nine patients, varying from 600 to 1,350, and was moderately increased in seven patients, ranging from 230 to 550. The resistance in four patients was not calculated because of insufficient data. Intracardiac shunting of blood from left to right was demonstrated in all 20 patients, the average shunt being 54%, with a range of 30 to 80%. In addition, right-to-left shunts determined by the dye-dilution technique [6] were present in six patients, with magnitudes ranging from 5 to 15%.

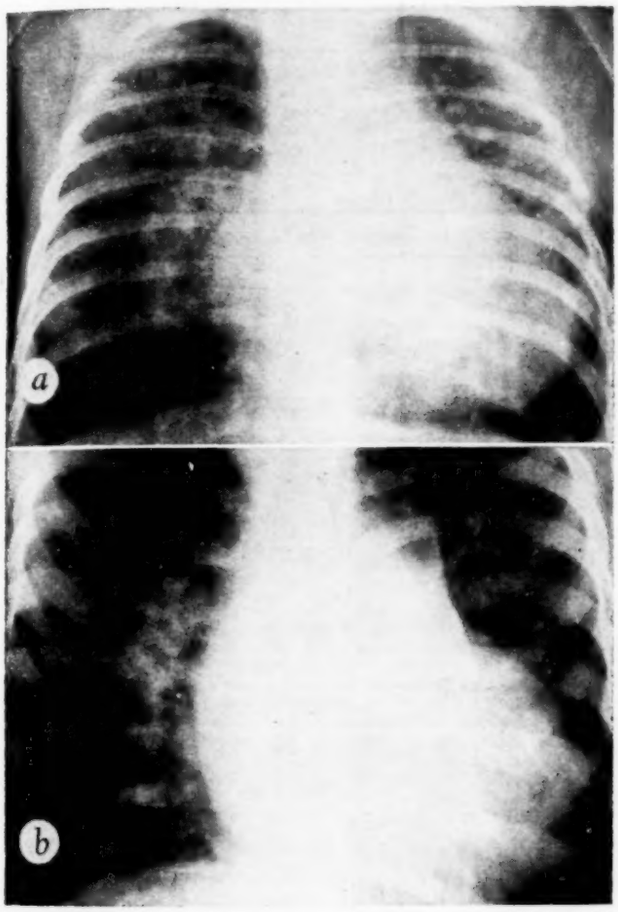

Fig. 1.—Pronounced cardiac enlargement and increased pulmonary vascular pattern in, *A*, 4-month-old infant and, *B*, 8-year-old boy with ventricular septal defect.

Surgical Management

Repair of the ventricular septal defect in each instance was achieved under direct visualization during open cardiotomy, the patient being maintained by extracorporeal circulation with a mechanical pump-oxygenator of the Gibbon type [7] (fig. 2). Adequate time was taken in each case for accurate intracardiac repair of the defect, the period of open cardiotomy varying from 10 to 45 minutes. Cannulas within the superior and inferior venae cavae diverted the venous blood from the patient to the

6. Swan, H. J. C.; Zapata-Diaz, J., and Wood, E. H.: Dye Dilution Curves in Cyanotic Congenital Heart Disease, Circulation **8**: 70-81 (July) 1953.

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TABLE 2.—*Laboratory Data on Twenty Surgical Patients with Ventricular Septal Defect*

Case No.	Age, Yr.	Systolic Blood Pressure, Mm. Hg: Pulmonary Artery	Systolic Blood Pressure, Mm. Hg: Radial Artery	Cardiac Index, Liter/Min./Sq. M.: Pulmonary	Cardiac Index, Liter/Min./Sq. M.: Systemic	Intracardiac Shunts of Blood, %: L-R*	Intracardiac Shunts of Blood, %: R-L*	Total Pulmonary Resistance, Dynes Sec. Cm.$^{-5}$	Result
1	5	45	60	†	†	55	0	†	Survived
2	6	80	100	9.2	3.8	60	0	1,350	Survived
3	½	70	80	†	†	†	†	†	Died
4	11	100	100	7.3	4.7	35	10	650	Died
5	4	25	80‡	11.4	6.0	50	0	†	Survived
6	12	50	105	4.6	†	70	0	380	Survived
7	1	65	85	†	†	60	0	†	Died
8	9	105	110	10.2	5.8	45	10	760	Survived
9	7	60	60	9.5	4.9	50	0	550	Survived
10	9	85	105	10.0	5.4	45	15	540	Survived
11	5	85	120	10.6	5.6	45	0	770	Survived
12	10	85	95	19.4	3.1	80	0	310	Died
13	5	100	120	7.7	†	†	5	1,070	Survived
14	8	50	100	12.1	4.3	65	0	260	Survived
15	4	80	90	12.7	6.4	50	0	680	Survived
16	29	105	105	7.8	2.6	70	0	490	Survived
17	3	80	105	7.9	5.6	30	5	1,120	Survived
18	10	95	115	5.0	1.9	60	10	940	Survived
19	11	60	130	4.5	2.0	55	0	600	Survived
20	3	30	85	8.8	3.4	60	0	230	Survived

* L-R = net left-to-right shunt as % of pulmonary flow. R-L = right-to-left shunt as % of systemic flow calculated from dye-dilution curves.

† Insufficient data for calculation.

‡ Systolic pressure in left ventricle. This patient had valvular pulmonary stenosis.

TABLE 3.—*Summary of Cardiac Catheterization Data on Twenty Surgical Patients with Ventricular Septal Defect*

Systolic Blood Pressure in Pulmonary Artery, % of Peripheral Arterial Pressure	No. of Patients
80 or more	11
60-79	4
40-59	3
Less than 40	2*
Total	20

* One of these patients had associated valvular pulmonary stenosis; the pressure in the right ventricle was 71/3 mm. Hg.

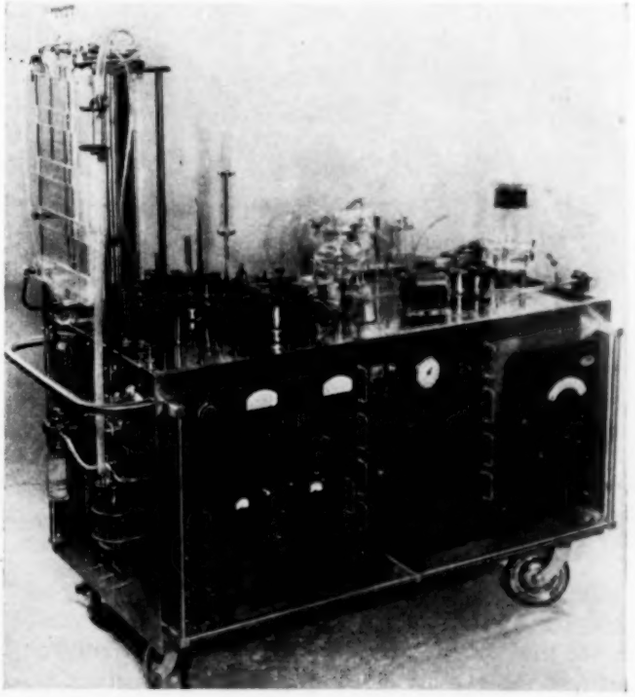

Fig. 2.—Pump-oxygenator (Gibbon type) constructed and used at the Mayo Clinic. Reprinted with permission from *Minnesota Medicine* (**39**: 1 [Jan.] 1956).

apparatus, and the arterial input to the patient was provided by a cannula inserted into the aorta through the previously divided left subclavian artery. Blood was collected from the open chambers of the heart by means of a specially designed sucker; this blood was returned to the apparatus (fig. 3).

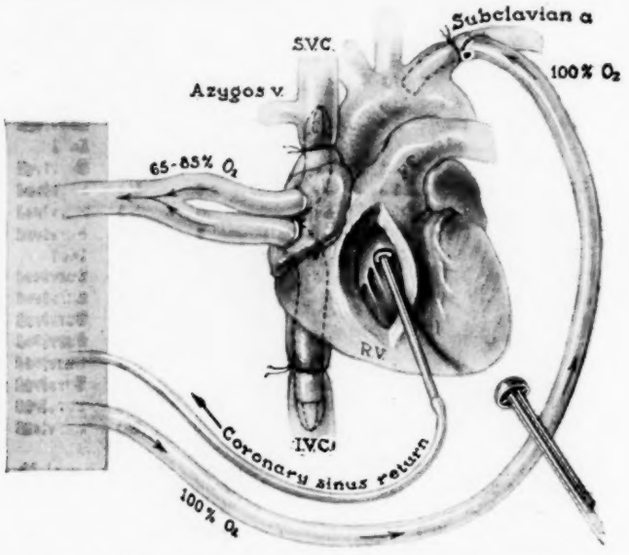

Fig. 3.—Cannulation of venae cavae and aorta for withdrawal of venous blood and perfusion of oxygenated blood from apparatus. The sucker for collecting blood from the open chamber of the heart is placed beneath the tricuspid valve, returning this blood to the apparatus.

Incision into the free wall of the right ventricle exposed the abnormal opening in the septum and permitted its repair (fig. 4). This was accomplished by direct suture in the first 3 patients, whereas this was done in the subsequent 17 patients by insertion of a nonab-

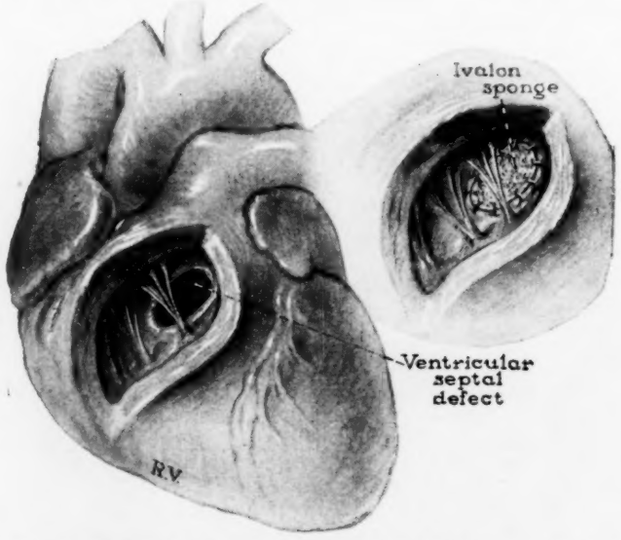

Fig. 4.—Right ventriculotomy and location of ventricular septal defect. Repair of the defect with use of a nonabsorbable polyvinyl (Ivalon) sponge is shown.

sorbable polyvinyl (Ivalon) sponge into the opening and placement of sutures through the sponge into the rim of the septal defect. During the time of extracorporeal circulation, the average flow of blood to the patient was 70 cc. per kilogram of body weight per minute. The oxygen saturation of the venous blood leaving the patient varied from 65 to 85%, while that of the blood returning to the patient from the pump-oxygenator was 100%.

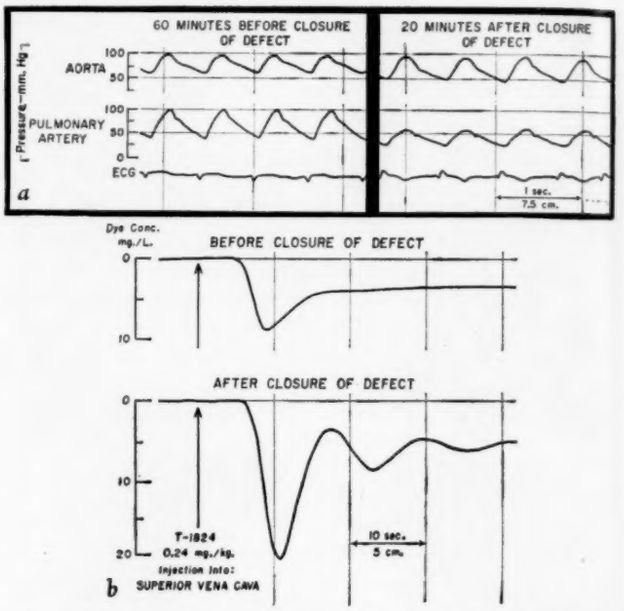

Fig. 5.—*A*, direct recordings of pressures in the aorta and pulmonary artery before and after closure of a ventricular septal defect in a 10-year-old girl. The pulmonary systolic arterial pressure decreased from 100 to 55 mm. Hg. *B*, dye-dilution curves before and after closure of a ventricular septal defect in an 8-year-old girl. The upper curve shows decreased deflection and a prolonged disappearance slope typical of a left-to-right shunt.[8] The lower curve, following repair of the defect, is normal, offering objective evidence that the defect is completely closed.

Dye-dilution techniques [8] were employed immediately before and after repair of the defect to study the effects of the closure, particularly in assessing the degree of completeness of the repair. Pulmonary arterial and pulmonary venous pressures were measured before and after

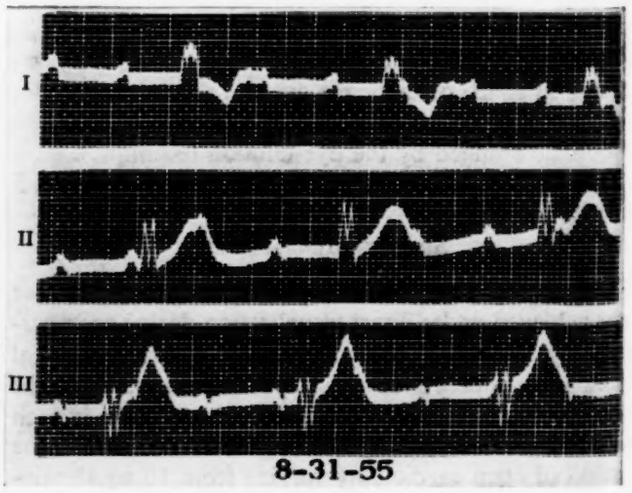

Fig. 6.—Electrocardiographic tracings from a 5-year-old girl, showing complete atrioventricular dissociation that occurred during the operation and persisted for 10 days before sinus rhythm spontaneously reappeared.

the surgical repair in many patients, while systemic venous and arterial blood pressure levels were recorded and electrocardiograms and electroencephalograms were made continuously throughout the operation in all patients.

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Results

Of the 20 patients, 16 survived and 4 died. Only one death has occurred in the last 13 operations. The perfusion was satisfactory, and the operation was successfully completed in every instance. The four children who did not survive died in the postoperative period as the result of pulmonary complications. The 16 living patients already have shown pronounced improvement in their general well-being. The preoperative heaving cardiac action has disappeared, the heart sounds have become less intense, and the loud second heart sound in the pulmonic area has diminished. The effect of surgical treatment on the cardiac murmurs has varied; the murmur has disappeared in some instances, whereas a soft to moderately loud systolic murmur has been noted in the pulmonic area in others. Improved appetite, a gain in weight, and increased exercise tolerance have occurred in each patient several weeks to months after the surgical procedure.

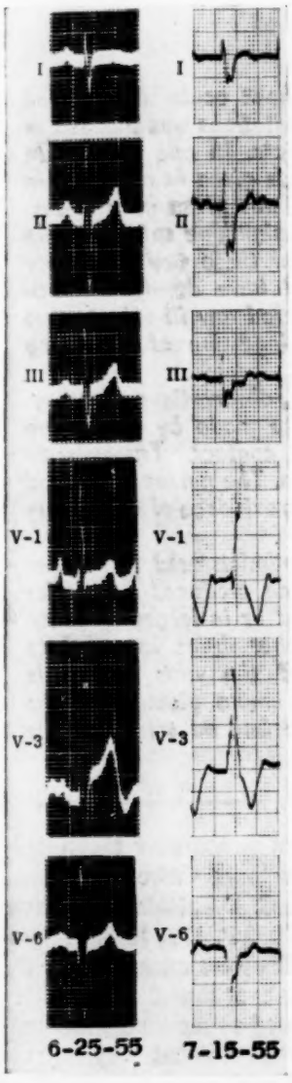

Fig. 7.—Preoperative and postoperative electrocardiograms demonstrating the right bundle-branch block that developed during closure of the ventricular septal defect in six patients.

In most cases, the pressure in the pulmonary artery has decreased substantially immediately after the repair of the defect, and dye-dilution curves have demonstrated the absence of abnormal intracardiac shunts (fig. 5). Postoperative studies utilizing cardiac catheterization have not yet been carried out.

Disturbances of the atrioventricular or intraventricular conduction mechanisms occurred in nine patients. Complete atrioventricular dissociation (fig. 6) was seen in three patients, but an effective ventricular rate was present in each, ranging from 45 to 65 beats per minute. The block was observed to occur at the time a suture was placed through the posteroinferior rim of the septal defect in the region thought usually to be traversed by the bundle of His. Sinus rhythm reappeared spontaneously after 5 days in one and after 10 days in another of the three patients who had complete heart block; the phase of recovery was associated with the electrocardiographic picture of interference dissociation in the latter patient. The third patient died on the sixth postoperative day, as the result of pulmonary complications associated terminally with an inadequate ventricular rate. Right bundle-branch block appeared in six patients at the time of operation and persisted throughout the postoperative period but apparently did not interfere with effective cardiac action and recovery (fig. 7).

Summary and Conclusions

Results of open cardiac operation, with use of a mechanical pump-oxygenator to bypass the circulation in a series of 20 patients with ventricular septal defects, indicate that the technique used is reproducible and that the surgical risk to the patient is acceptably low, considering the severity of the condition. Of the 20 patients having the operation, 16 survived. The predicted risk is dependent on age, general health, and the presence or absence of cardiac failure and of pulmonary complications. Increasing experience already has lessened the risk of operation, as indicated by the fact that just one death has occurred in the last 13 operations.

It is believed that children or adults who have significant symptoms resulting from ventricular septal defects associated with left-to-right shunts should have the defects closed, even in the presence of moderate to severe pulmonary hypertension. Selection of candidates for operation should depend on accurate physiological studies by cardiac catheterization, with special reference to determinations of pulmonary and systemic vascular resistances and the consequent magnitude and dominant direction of intracardiac shunts. Operation should be considered in a patient with a small or a moderate right-to-left shunt if there is an associated large left-to-right shunt and increased pulmonary blood flow. Analysis of the ventricular balance, as demonstrated by electrocardiography, has indicated that, so far, those patients who have definite left ventricular hypertrophy in addition to right ventricular hypertrophy tolerate closure of the ventricular septal defect better with respect to survival and rapid postoperative recovery than do those without significant degrees of left ventricular hypertrophy. This fact no doubt reflects the hemodynamic situation regarding the intracardiac shunts of blood.

Diabetes Mortality.—The death rate from diabetes in the United States, adjusted for changes in the age composition of the population, has decreased somewhat in recent years—from 15.4 per 100,000 in 1949 to 14.0 in 1953, or by 9 per cent. . . . Of considerable importance is the fact that general health conditions in the country have been exceptionally good in this period, and there has been relative freedom from severe and widespread outbreaks of respiratory disease. Since the impact of serious infections is greater on diabetics than on most persons with other chronic disorders, the relatively low incidence of acute respiratory disease is reflected in the mortality from diabetes. Moreover, the advances in chemotherapy have been of great benefit in the management of such infections among diabetics. The trend of the diabetes death rate in recent years also gives some indication of the improvement in control of the disease resulting from the increased emphasis on early diagnosis and from advances in treatment. . . . Although the mortality from diabetes now accounts for less than 2 per cent of the total deaths in the population, the disease is more important than is indicated by this low proportion. Deaths ascribed to diabetes now constitute probably less than half of the total among diabetics. Most of the deaths among them, whether or not ascribed to the disease, are accounted for by arteriosclerotic complications.—Diabetes Mortality in Recent Years, *Statistical Bulletin Metropolitan Life Insurance Company*, October, 1955.

CLINICAL INVESTIGATIONS ON ATTENUATED STRAINS OF POLIOMYELITIS VIRUS

USE AS A METHOD OF IMMUNIZATION OF CHILDREN WITH LIVING VIRUS

Hilary Koprowski, M.D., Thomas W. Norton, Pearl River, N. Y., George A. Jervis, M.D., Thiells, N. Y.
Thomas L. Nelson, M.D., Eldridge, Calif., David L. Chadwick, M.D., San Francisco
Doris J. Nelsen, Pearl River, N. Y.
and
Karl F. Meyer, M.D., San Francisco

• Alimentary infection without acute disease and without neurological manifestations was induced in two series of human subjects. In one series, SM type 1 poliomyelitis virus was given in capsules; in the other, TN type 2 virus was given in milk suspension. Altogether, 225 nonimmune subjects have received one or the other of these two viruses for immunization purposes; all have developed antibodies, and none have suffered any ill-effects that could be ascribed to the ingestion of the living poliomyelitis virus.

Within the isolation unit, observations on transmissibility of the virus were made by setting up conditions that permitted contact. Transmission occurred in 5 of 15 contacts. The nurses who cared for these patients showed no evidence of alimentary infection.

When the viruses were administered simultaneously, the type 1 virus alone produced antibodies unless type 2 was given first or in larger amounts. Mercurous chloride and other drugs intended to suppress fecal excretion of the virus had little effect. Administration of gamma globulin at the time the virus was ingested had no effect on the antibody response.

During the past five years, evidence has been accumulated indicating that man can be immunized successfully against poliomyelitis by oral administration of live, attenuated viruses.[1] The purpose of this presentation is to review briefly the results obtained previously and to report the outcome of clinical trials carried out on a much broader scope.

Résumé of Past Experience

On Feb. 27, 1950, the first human subject received orally a dose of live, attenuated TN (type 2) strain of poliomyelitis virus.[1a] Up to the time of the clinical trials to be reported in this paper, 118 individuals had been fed the same strain for immunization purposes and 37 had received the SM (type 1) strain. Properties of the strains will be described below. The organization of the previous clinical trials followed an established pattern.[1c] Presence of antibodies was determined in the blood specimens, and only those individuals were included in the trial who showed absence of antibodies to the type of virus to be administered. In addition, an attempt was made to secure subjects who had no antibodies against any of the three types of virus used. Virus was always given by the oral route, either in milk or in a hard gelatin capsule (type 1 only).[1c] All individuals who had ingested the virus were quarantined and subjected to rigid clinical observation. Tests for the isolation of virus were made on stool specimens collected daily (and then pooled) and, occasionally, on blood samples. The development of antibodies was determined in serum samples drawn at definite intervals after the administration of the virus.

None of the 155 subjects, the majority of whom were children, showed any signs of sickness that could have been attributed to the ingestion of virus. No virus was isolated from the blood of individuals who received either type 1 or type 2 virus.[2] Throat swabs were taken daily in eight subjects who drank a "milk shake" containing type 1 (from $10^{2.8}$ to $10^{4.9}$ T. C. $D._{50}$ [infectious tissue culture doses]) and type 2 ($10^{5.0}$ P. $D._{50}$ [mouse paralytic doses]) strains. The swabs were examined for the presence of virus, and none was ever found. When either mice or tissue cultures were used as mediums, the noncytopathogenic type 2 strain was isolated only on rare occasions from fecal material and, even then, only in concentrations never exceeding $10^{1.0}$ P. $D._{50}$ per gram of fecal material. In contrast, the cytopathogenic type 1 SM strain was isolated from the stools of every subject who ingested the virus.[1c]

Evidence accumulated in the course of these trials has helped to elucidate certain aspects of the behavior of the viral agents in the human host as compared to the animal host, but several questions still remained unanswered. These were (1) the degree of susceptibility of the human alimentary tract to infection with attenuated strains, (2) the contagious properties of attenuated viruses, (3) the possibility of controlling excretion of virus from the human alimentary tract, (4) the effect of the simultaneous administration of attenuated viruses and immune serum globulin, (5) response of individuals previously immunized with a given strain to reexposure to the same

From Viral and Rickettsial Research, American Cyanamid Company Research Division, Lederle Laboratories (Dr. Koprowski, Mr. Norton, and Mrs. Nelsen); Research Department, New York State Department of Mental Hygiene, Letchworth Village (Dr. Jervis); Sonoma State Hospital, California State Department of Mental Hygiene (Dr. Nelson); Department of Pediatrics, University of California School of Medicine (Drs. Nelson and Chadwick); and George Williams Hooper Foundation, University of California School of Medicine (Dr. Meyer).

1. (*a*) Koprowski, H.; Jervis, G. A., and Norton, T. W.: Immune Responses in Human Volunteers upon Oral Administration of Rodent-Adapted Strain of Poliomyelitis Virus, Am. J. Hyg. **55**: 108, 1952. (*b*) Koprowski, H.: Immunization of Man Against Poliomyelitis with Attenuated Preparations of Living Virus, Ann. New York Acad. Sc. **61**: 1039, 1955; (*c*) Living Attenuated Poliomyelitis Virus as an Immunizing Agent in Man, South African M. J. **29**: 1134, 1955. (*d*) Koprowski, H.; Jervis, G. A., and Norton, T. W.: Administration of Attenuated Type I Poliomyelitis Virus to Human Subjects, Proc. Soc. Exper. Biol. & Med. **86**: 244, 1954.

2. Koprowski, H., in Poliomyelitis, World Health Organization Monograph Series 26, New York, Columbia University Press, 1955, p. 335.

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strain of attenuated viruses, and (6) the possibility of overcoming interference between different strains of poliomyelitis virus. Investigation of these problems was undertaken in the present trial.

Material, Methods, and Organization of Clinical Trial

Strains of Virus.—Three attenuated strains of virus were used: type 2 TN [1a] and MEF 1 [3] strains and type 1 SM [4] strain. The TN strain is a rodent-adapted type 2 virus. It is completely apathogenic when injected intracerebrally in monkeys,[1c] but, if it is administered in high concentrations by intraspinal inoculation, it occasionally may cause paralysis in a monkey.[1c] The TN strain is noncytopathogenic for tissue culture–grown fibroblasts or epithelium of either simian or human (normal or neoplastic) origin.[1b] Its presence had to be determined through intraspinal inoculation of adult laboratory mice of the Swiss albino strain. Two pools of the TN strain were used in the present trial, one prepared as mouse brain and cord suspension representing the 27th mouse passage of the virus in PRI strain of mice since its original isolation [1b] and the other made from cotton rat brain and cord representing 8 mouse brain passages followed by 2 cotton rat brain passages.[1a] The latter type of material was used in the previous trial reviewed above, and in the present test it was given only to a group of subjects who had been immunized with the same viral preparation three years before.

The SM strain, representing type 1 virus, is also a rodent-adapted strain.[4] It can be maintained, with the help of alternating passages through monkey kidney cultures, in chick embryo tissue cultures. The material used in the present trial was made from chick embryo tissue culture suspension. It represented the 26th mouse spinal cord passage, plus 10 passages in monkey kidney tissue cultures and 14 in chick embryo tissue cultures. Further passages in chick embryo tissue cultures were alternated occasionally with monkey kidney tissue cultures. This was necessitated by the impossibility of maintaining the passage serially in chick embryo after the 14th subculture. The SM strain is cytopathogenic for monkey kidney epithelium, and its presence was determined either by observation of cytopathic changes in tissue culture tubes or by counting the viral plaques observed on monolayers of epithelium derived from monkey kidney.[5] The SM strain is apathogenic when injected intracerebrally in monkeys, but when injected intraspinally in high concentration it will cause paralysis of some of the inoculated animals.[1c]

Administration of Viruses to Human Subjects.—The type 1 SM strain was administered to all subjects in the present trial in capsule form, prepared in the following way. Virus-containing material was thawed out from the frozen state and, either undiluted or diluted to a desired concentration in balanced salt solutions, was mixed in equal proportion with polyethylene glycol 400. It was then placed in a hard gelatin capsule in 0.5 ml. amounts. The outside of the capsule was rinsed thoroughly in running tap water. Each subject swallowed two such capsules, consuming at the same time 8 ml. of milk. The TN (type 2) strain was administered to all subjects, with the exception of three, in a liquid form. Nine milliliters of the respective dilution of virus was mixed with 15 ml. of milk and given to the patient in a single drink. In addition, three subjects received the virus in capsule form, prepared in the same manner described for type 1 virus.

Determination of the amount of virus actually administered to each participant was done after the virus-containing material was mixed with diluting fluid; i. e., polyethylene glycol in the case of SM strain and milk in the case of TN strain. The amount of SM virus ingested was expressed in terms of plaque-forming particles of virus.[5] The amount of TN strain was expressed as mouse paralytic doses of mice injected intraspinally.

Locale of Trial and Choice of Patients.—A state institution for mentally defective children was used for the trial purposes. The inmates were subjected to immunization procedures after permission to do so was secured from the state departments of mental hygiene and public health and from the parents of each child. Parental permissions were obtained in person by a pediatrician, who explained at the time what the project entailed. A newly constructed, and until then uninhabited, building was designated by the institution for the purpose of the trial. As soon as the patients were fed the virus, they were isolated in this building, which was regarded as an "infected area" by the rest of the institution. Access to the building was restricted to a minimum number of persons required to work within it. All materials and objects leaving the contaminated areas were disinfected (by autoclaving or by chemical means). Additional isolation procedures were applied to individual areas within the building.

All of the subjects were located in three areas, known as ward A, ward B, and "isolation" (fig. 1). Each group was completely separate from the other groups and from the rest of the building. Each area had an entrance from the central hall of the building, where special technique was enforced to prevent contamination of the central hall and of the remainder of the building. In addition, there were doors leading from each area to an outside ramp. Nurses engaged in direct care of subjects were on duty in one contaminated area only. It was occasionally necessary to shift a nurse from one area to another, but this was never done during the course of that nurse's working day. The only personnel who went from one area to another were the head nurse and four physicians and, on rare occasions, a maintenance man.

All persons entering a contaminated area observed strict isolation technique, donning a gown on entering and discarding it on leaving. In addition, the shoes worn in a contaminated area were not worn in the remainder of the building or on the state hospital grounds. Personnel carefully changed shoes while stepping out of the doorways of contaminated areas. Hands were disin-

3. Roca-Garcia, M., and Jervis, G. A.: Experimentally Produced Poliomyelitis Variant in Chick Embryo, Ann. New York Acad. Sc. **61**: 911, 1955. Roca-Garcia, M.; Moyer, A. W., and Cox, H. R.: Poliomyelitis: Propagation of MEF 1 Strain of Poliomyelitis Virus in Developing Chick Embryo by Yolk Sac Inoculation, Proc. Soc. Exper. Biol. & Med. **81**: 519, 1952.

4. Koprowski, H.; Jervis, G. A.; Norton, T. W., and Pfeister, K.: Adaptation of Type I Strain of Poliomyelitis Virus to Mice and Cotton Rats, Proc. Soc. Exper. Biol. & Med. **86**: 238, 1954.

5. Dulbecco, R., and Vogt, M.: Plaque Formation and Isolation of Pure Lines with Poliomyelitis Viruses, J. Exper. Med. **99**: 167, 1954.

fected with Wescodyne (a mixture containing as active ingredients polyethoxy polypropoxy ethanol-iodine complex, 7.75%, and nonyl phenyl ether of polyethylene glycol-iodine complex, 3.75% [provides 1.6% available iodine]), which was used at a 1% concentration, previously found to be virucidal. This was followed by liberal use of soap and water. This procedure was strictly adhered to before persons left contaminated areas.

Food was distributed by wheeling a loaded cart up to the opened door of the contaminated area and transferring the food to a second cart within in such a way as to prevent contamination of the clean food cart and the kitchen helper. Clean linen, clothing, diapers, and supplies were passed in from the central hall in a similar

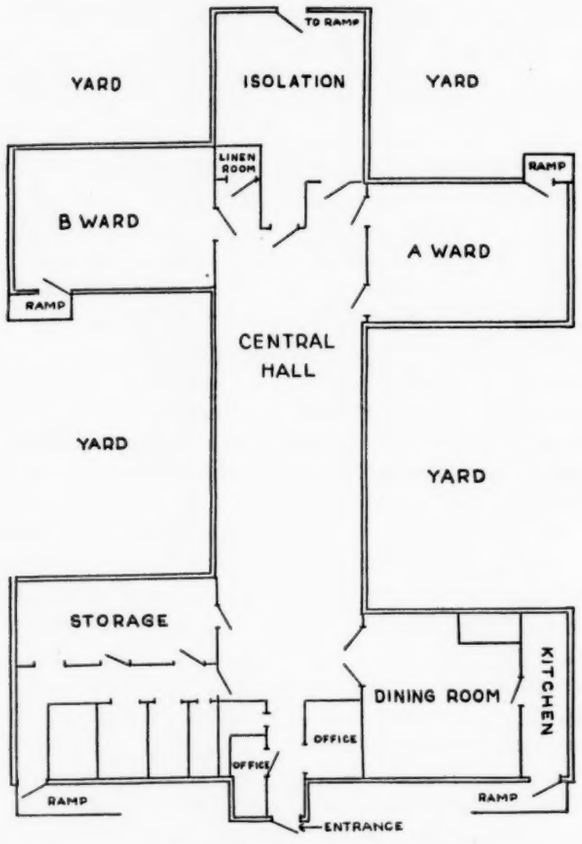

Fig. 1.—Location of subjects.

manner. All dirty dishes, left-over food, and similar objects were disinfected with Wescodyne before being handed out of the contaminated areas through outside doors. Dirty linen and clothing were placed in laundry bags, passed to attendants through outside doors, and taken immediately to an autoclave for sterilization prior to laundering. No material of this type was ever taken through the central hall.

In general, the greatest care was used in handling and disposing of feces and fecally contaminated objects. Such things as nurses' gowns, bedding, and clothing were disinfected when there was any suspicion of fecal contamination. The only objects that were removed from contaminated areas through the inner doors were the regular stool and blood specimens, occasional miscellaneous diagnostic specimens collected in the course of incidental illnesses among the subjects, and used syringes and needles. Stool specimens, in tightly closed containers, were handed through the door to a laboratory technician. No other person handled these specimens in the clean areas. Such specimens were carried directly to the laboratory, where they were prepared for shipment. Each individual had his own thermometer and tooth brush. Thermometers were kept in separate labeled tubes containing Wescodyne; tooth brushes were hung separately in a rack in the bathroom.

Subjects for the present trial were selected from a larger group of individuals whose blood specimens were examined for the presence of antibodies against poliomyelitis by tissue culture neutralization tests. Subjects lacking antibodies to the type of virus to be administered were chosen. In several instances, subjects were secured who had no antibodies against any of the three types of virus. On the eve of the trial, blood specimens were secured from all individuals scheduled for the tests to determine whether they had acquired antibodies during the time interval between the first bleeding and the start of the trial. Seventy children participated in the trial; all were between the ages of 6 and 15 years. Nineteen of these, who had been immunized three years before,[6] were brought into the study at a later date.

Medical Supervision.—The supervisory staff consisted of two pediatricians, one full-time neurologist, a head nurse, a staff of registered nurses, and personnel trained in laboratory work with viruses, particularly poliomyelitis virus. The duties of the medical staff were to provide necessary care for all subjects; to observe, diagnose, and document all illnesses that developed during the study; and to evaluate the possible relationship of such illnesses to infection with the ingested virus or to the effects of drugs used to suppress alimentary infection with the poliomyelitis virus. Temperatures were taken every 12 hours. There was continuous observation by registered nurses. Each child was examined twice daily by the pediatricians and neurologist, with a complete physical examination of all subjects showing disturbances such as temperature elevation, vomiting, or other signs noted by nurses. Diagnostic laboratory studies were done as deemed necessary by the pediatrician.

Laboratory Studies.—Laboratory studies included isolation of poliomyelitis virus from stools and neutralization tests.

Isolation of Poliomyelitis Virus from Stools: Stools from every subject in the trial were collected daily. An 8 to 12 gm. sample of each stool was then placed in a plastic centrifuge tube and kept in chopped ice in the ward for one to four hours. After that period, sterile distilled water was added to a volume equivalent to four times the weight of the stool. The tubes were placed in a freezer kept at a temperature below –40 C. Twice a week the tubes were put in a shaking machine for a period of 18 hours at 4 C. Equal amounts of suspension representing specimens collected from the same individual over a four-day period were pooled. (The "pooling" of stool samples was not done in the case of subjects who were contacts of children excreting virus. In these cases,

6. Koprowski, H.; Jervis, G. A.; Norton, T. W., and Nelsen, D. J.: Further Studies on Oral Administration of Living Poliomyelitis Virus to Human Subjects, Proc. Soc. Exper. Biol. & Med. **82**: 277, 1953.

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each stool specimen was processed for virus isolation.) The pool was centrifuged under refrigeration for 60 minutes at 11,000 rpm. The supernatant fluid was filtered through a small paper filter, and enough penicillin and streptomycin were added to the filtrate to equal a concentration of 1,000 units of penicillin and 20 mg. of streptomycin per cubic centimeter and the pH adjusted to about 7.4 if necessary. The supernatant fluid was then either used for inoculation of mice and tissue culture tubes or, if toxic to tissue, submitted to another cycle of centrifugation at 14,000 rpm for 60 minutes before being used.

Three to six monkey kidney tissue culture tubes were inoculated, and 12 mice were injected intraspinally with each specimen. If no cytopathogenic effect was observed within seven days after the inoculation of the tissue culture, aliquots of tissue culture fluids were subinoculated into another set of tissue culture tubes. Negative results of the second passage prompted another, the third and last subculture. If mice did not show signs of paralysis by the seventh day after inoculation, two mice of each group were killed and a 10% suspension of spinal cord tissue injected intraspinally into eight additional mice. If no paralysis was observed, the same procedure was repeated, with two of the eight mice used to provide the suspension for inoculation. If three "blind passages" made either in tissue culture or in mice failed to reveal the presence of virus, the respective inoculum was recorded as virus-free. In many cases the isolates were identified through a neutralization test against either type 1 or type 2 specific antiserum.

Neutralization Test: The tissue culture neutralization test technique described by Salk and others [7] was adopted, with use of serial fourfold dilutions of antiserum mixed with 100 to 1,000 T. C. D_{50} of the respective virus type. In several cases the results of this test were checked by a roller tube test in which the presence of cytopathic lesions was observed directly under the microscope [8] instead of through the observation of pH changes. The latter type of test was used for identification of viruses isolated from the feces of all subjects.

Results

Clinical Studies.—It may be stated emphatically that no acute disease with neurological manifestations was observed during the entire period of the study. Specifically, meningismus, flaccid paralysis, and changes in neurological findings were not observed. Clinical problems that presented themselves in the course of the investigation were chiefly related to the preexisting diseases of the subjects and may be summarized in the following way. Neurological diseases, in addition to mental deficiency, were present in a large majority of subjects. These diseases included cerebral dysgenesis, hydrocephalus, birth anoxia and trauma, meningitis sequelae, cerebral hemorrhage, phenylpyruvic oligophrenia, toxoplasmosis, and at least one degenerative disorder of unknown etiology (possibly juvenile amaurotic familial idiocy). Abnormal neurological findings among subjects were all of the "upper motor neuron" or basal ganglia type and included all types and degrees of spastic paralysis, athetosis, chorea, and related manifestations of brain damage. Many children had contractures and muscle wasting, but none exhibited flaccid paralysis. It was assumed that if any disease were caused by the ingested virus it would resemble poliomyelitis and would result in fever, stiff neck and back, and possibly weakness or flaccidity of muscles. It was presumed that it would be possible to detect these manifestations even in severely spastic subjects.

Chronic regurgitation of food was manifested by a number of subjects, making the evaluation of vomiting by any one of them somewhat difficult. In general, vomiting in these children was not considered a symptom of acute disease unless it was accompanied by other manifestations. Two subjects had chronic otitis media, both of these having one flare-up during the study. At least two subjects were carriers of Giardia lamblia; one of them had frequent loose stools throughout the study. Poor oral hygiene, with gingivitis and, in some instances, frank pyorrhea, was present in a large number of subjects. These conditions improved considerably during the course of the study. Chronic rhinitis was present in many subjects, especially among those with Mongolism. Molluscum contagiosum was present in some subjects. Over half of the individuals previously had had convulsive seizures, and four had seizures during the course of the study. Because of preexisting conditions, a large number of the participants in the trial were receiving regular medicaments at the start of the study. Drugs being administered included anticonvulsants and sedatives (phenobarbital, diphenylhydantoin [Dilantin] sodium, and Mesantoin [3-methyl-5,5 phenylethylhydantoin]), antispasmodics (trihexyphenidyl [Artane] hydrochloride), and vitamins (Dispadal suspension and solution, vitamin B complex).

In addition to the chronic neurological conditions, several subjects developed acute diseases, all of which were easily and definitely diagnosed. These included the common cold; pharyngitis caused by beta-hemolytic Streptococcus, pneumococcus, and Micrococcus (all confirmed by laboratory isolation of the causative agent); conjunctivitis caused by Hemophilus influenzae; and rubella and varicella. Presence of these diseases necessitated administration of certain medicaments. These included an antipyretic (aspirin), antibiotics (penicillin intramuscularly and erythromycin and oxytetracycline [Terramycin] orally), a vasoconstrictor (ephedrine orally), and an antihistaminic (diphenhydramine [Benadryl] orally). Prompt diagnosis of the acute diseases and good knowledge of the preexisting conditions permitted the investigators to consider the administration of the live, attenuated SM and TN strains as a definitely harmless procedure.

Two months after the first administration of poliomyelitis virus to the clinical trial group, two children already removed from the poliomyelitis study developed pharyngitis and organisms resembling Corynebacterium diphtheriae were isolated from throat cultures. The signs

7. Salk, J. E.; Youngner, J. S., and Ward, E. N.: Use of Color Change of Phenol Red as the Indicator in Titrating Poliomyelitis Virus or Its Antibody in a Tissue-Culture System, Am. J. Hyg. **60**: 214, 1954.

8. Robbins, F. C.; Weller, T. H., and Enders, J. F.: Studies on Cultivation of Poliomyelitis Viruses in Tissue Culture: Propagation of Poliomyelitis Viruses in Roller-Tube Cultures of Various Human Tissues, J. Immunol. **69**: 673, 1952.

consisted of fever of 38 C (100.4 F) and a slightly injected pharynx with shotty cervical nodes. None of the children appeared unduly ill. In addition to these two apparently chronic carriers, the same organisms were recovered from a total of 17 persons in the building. Five of these patients (subjects 46 and 47, fig. 2; subject 6, fig. 3; and subjects 18 and 33, fig. 4) were still excreting poliomyelitis virus. Symptoms in these patients consisted of a mild sore throat and slightly tender cervical lymph nodes. No fevers were observed, and no laryngitis or involvement of pharyngeal membranes was noticed. Treatment of the 17 cases with antibiotics (tetracycline [Achromycin] or oxytetracycline) resulted in successful eradication of the organism in three to

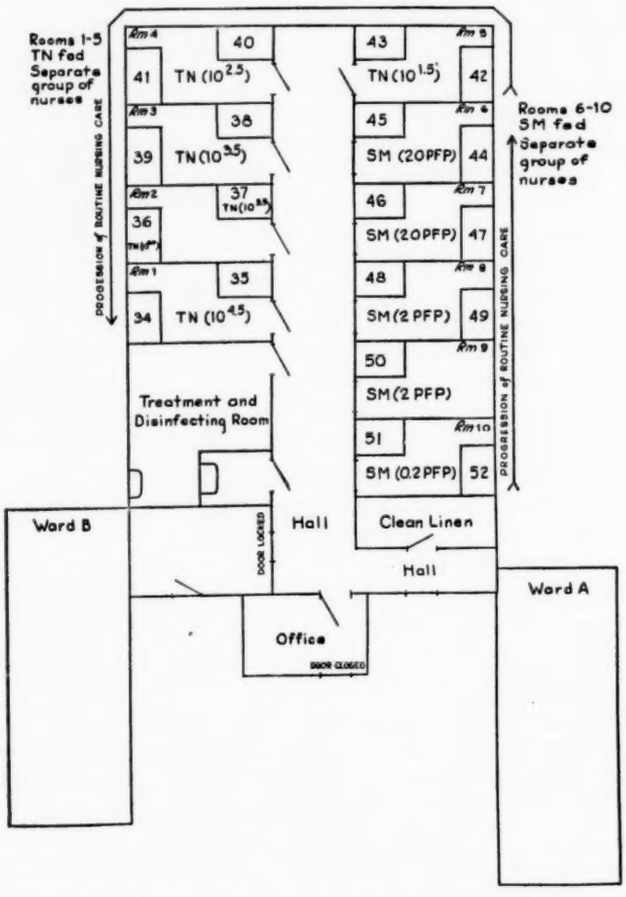

Fig. 2.—"Isolation area" virus titration trial group. PFP, plaque-forming particles.

four days. More than two weeks after the onset of the first case of this pharyngitis, booster injections of diphtheria and tetanus toxoids with pertussis vaccine, combined, were administered to seven subjects who were still excreting the administered strain of poliomyelitis virus (subjects 1, 5, 6, 7, 23, 27, and 33, fig. 3 and 4). The expected reactions consisted of low-grade fever in a few patients and transient soreness at the injection site.

Susceptibility of Human Alimentary Tract to Infection with Attenuated Strains.—Subjects who were subjected to the "virus titration" trial were kept in the "isolation area" (fig. 2). This area was divided into two sections, each containing five separate rooms occupied by patients who had received different virus dilutions, as depicted in figure 2. Separate groups of nurses served the two parts of the area but used a common hallway, a common storage room for clean linen and gowns, and a common disinfecting area for contaminated materials. The main isolation barrier was at the door of each room, and gown and hand disinfection techniques were observed at these points. Contaminated materials were collected in paper bags or Wescodyne-filled buckets within each room, and great care was exercised to avoid contamination of the hall and other areas. For routine care, nurses worked from the rooms of patients administered the least amount of virus to the rooms of those administered the most virus.

The results of the trial are shown in tables 1 and 2. As measured by the rate of alimentary infection and by antibody response, all subjects who ingested an equivalent of 20 plaque-forming particles of type 1, SM strain,

TABLE 1.—*Relationship Between Dosage and Alimentary Infection with SM Type 1 Virus Given in Capsule Form*

P. F. P.* of Virus Fed	Subject†	Duration of Alimentary Infection, Days	Antibody Titer ‡ After Virus Feeding		
			13 Days	27 Days	60 Days
200	16	2-56	1.2	1.8	2.4
	18	1-56	1.2	1.8	2.4
	19	5-77	<0.9	1.2	2.4
	20	5-21	<0.3	2.4	1.8
20	44	4-21	2.4	2.4	1.8
	45	8-34	1.8	2.25	2.4
	46	3-44	0.6	1.8	1.8
	47	3-75	1.2	1.8	2.4
2	48	1-44	0.6	1.8	1.8
	49	3-30	1.2	1.8	2.4
	50	None	0	0	0
0.2	51	None	0	0	0
	52	None	0	0	0

* P. F. P., plaque-forming particles.
† All subjects had no type 1 and type 2 antibodies prior to feeding.
‡ Expressed as common logarithms.

became infected with the virus (table 1). Two out of three subjects who were fed the equivalent of 2 plaque-forming particles of virus also became infected. An amount corresponding to 0.2 plaque-forming particles failed to induce alimentary infection. Whether this is a true experimental finding depends on several factors that remain to be clarified. It may be possible that the diluent used in the preparation of the virus capsule may have interfered in some way with the determination of virus concentration in tissue culture. It may also be of importance to count the number of plaques of virus grown on a monolayer of epithelium of human origin [9] rather than on one of simian origin. There is also the possibility that the virus administered in a capsule may have been placed in immediate contact with a particularly susceptible segment of the intestinal tract, possibly some lymphoid tissue such as Peyer's patches.[10]

Results of the trial in which the type 2 TN virus was used are shown in table 2. The laboratory determination of the infectivity of the inoculum had to be done in mice because of the noncytopathogenic character of the virus strain.[1b] This method is much less exact than that employed for type 1 virus. Again, however, an individual

9. Kibrick, S.: Comparative Susceptibility of Roller Tube Cultures of Different Tissues to Poliomyelitis Virus, Ann. New York Acad. Sc. **61**: 822, 1955.

10. Bodian, D.: Emerging Concept of Poliomyelitis Infection, Science **122**: 105, 1955.

was found susceptible to a dose as small as 300 ($10^{2.5}$) P. $D._{50}$ of virus, although one or possibly two subjects escaped infection with an amount of virus 10 times greater. Antibody response was used as the criterion of infection, since, as was mentioned before, excretion of this virus occurs sporadically and in low concentration. Administration of the virus in capsule form to three persons (subjects 43, 55, and 51) resulted in a late formation of homotypic antibodies as compared to those (subjects 34, 35, and 36) who received $10^{4.5}$ P. $D._{50}$ in milk suspension. No conclusions can be drawn from this trial on the results of administration of type 2 virus in capsule form. A clinical study, similar to the one performed with type 1 virus, in which falling concentrations of type 2 virus were administered, would have to be performed.

TABLE 2.—*Relationship Between Dosage and Alimentary Infection with TN Type 2 Virus Given in Milk Suspension*

P. $D._{50}$* of Virus Fed†.	Subject‡	Duration of Alimentary Infection, Days	Antibody Titer After Virus Feeding		
			13 Days	27 Days	60 Days
4.5	34	None	2.4	2.4	...
	35	12-14	0.8	2.8	...
	36	11-16; 21-22	1.8	2.4	...
3.5	37	None	0	0	0
	38	None	0.3	2.4	...
	39	None	0.3	0.6	0.6
2.5	40	12-14; 18-22	2.4	2.8	...
	41	None	0.8	0.6	1.2
1.5	42	None	0	0	0
	43	None	0	0	0
4.0	43 §	None	0	Trace	1.2
	55 §	None	0.6	0.6	1.2
	51 §	7-32	0	1.8	1.8

* P. $D._{50}$, mouse paralytic doses.

† Expressed as common logarithms.

‡ All subjects with the exception of subject 51 had antibodies against types 1 and 3 but no antibodies against type 2 before administration of the virus; subject 51 had no antibodies against types 1 and 2.

§ These individuals were fed the virus in capsules at a later date in the trial than the ones above. Subjects 43 and 51, who had no type 2 antibodies at this time, were refed virus.

Again, taking antibody response as a criterion of infection, it seems that the intestinal tract of human subjects responds more promptly to infection with the cytopathogenic type 1 virus than with the noncytopathogenic type 2 strain. The advantage of the sporadic appearance, at low concentration, of type 2 virus in the excreta over the "constant" excretion of type 1 is obvious from the point of view of contagiousness of the attenuated strains.

Attenuated Virus as a Contagium.—Today the main objection of public health authorities to the more widespread use of live, attenuated viruses in clinical trials is the fear of contagion. Without going into details regarding the relative merits of divergent opinions, some facts will be presented for consideration. There are formidable odds against the contagiousness of the TN strain because of the character of the virus. Evidence accumulated from the successive trials conducted during the past five years [11] has indicated that the TN type 2 virus is not contagious; i. e., cannot be passed from one subject to another. However, the cytopathogenic SM type 1 virus, which is excreted from the human intestinal tract more regularly and at higher concentrations,[1c] poses another problem.

Six children who had no antibodies against types 1 and 2 were fed the SM and TN strains simultaneously in concentrations stated in table 3. Type 1 was administered

TABLE 3.—*Direct Contact—Transmission of Attenuated Poliomyelitis Virus from Man to Man*

Groups and No. of Subjects in Group	No. Pre-feeding Anti-body to Types	Type Fed	Subject	Duration of Intestinal Carriage of Type 1*	Type 1 Antibody Response After Virus Fed		
					13 Days	27 Days	60 Days
Donors 6	1, 2	1, 2‡	4	1-60	1.0	1.2	1.8
			6	1-4; 11-69 74-87; 98-104	1.2	1.2	1.9
			2	4-65	0.6	0.8	2.4
			12	5-16	1.4	1.2	1.8
			8	6-9; 24	<0.3	0.6	1.2
			10	6-8; 16-26	1.2	1.2	1.8
Contacts 8†	1, 2, 3	None	3	4-66	<0.3	1.2	2.4
			1	10-85	<0.3	0.8	1.2
			11	11-98	<0.3	1.8	1.8

* No intestinal carriage of type 2.

† Five subjects did not become infected.

‡ 200 plaque-forming particles of SM strain and 90,000 mouse paralytic doses of TN strain administered.

in capsule form; type 2 was given in milk. None of the six was found to excrete type 2 virus, but all became intestinal carriers of type 1 virus. These six subjects, comprising group 1, were kept in close contact with eight

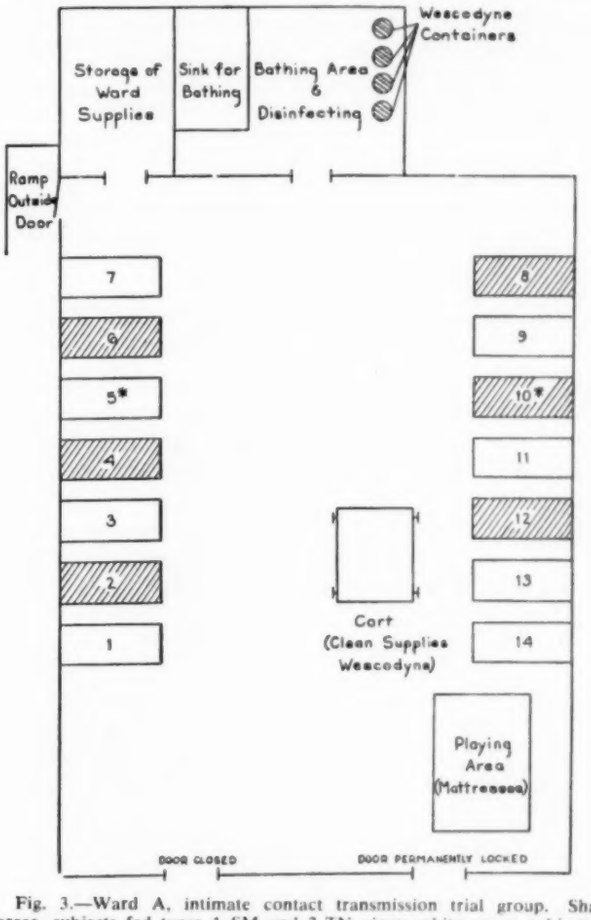

Fig. 3.—Ward A, intimate contact transmission trial group. Shaded areas, subjects fed types 1 SM and 2 TN virus; white areas, subjects fed no virus. Asterisks indicate hydrocephalic subjects.

other children, forming group 2, who had no antibodies against any of the three types of poliomyelitis virus in their blood specimens prior to the trial. Both groups were kept in ward A of the building (fig. 1). The arrange-

11. Footnotes 1c and 6.

ment of cribs and the general layout of the ward are shown in figure 3. Before discussing the actual results, it should be stressed that it was impossible to achieve a "normal contact" environment because all of the children in this area were fecal soilers. Also, as the majority of children

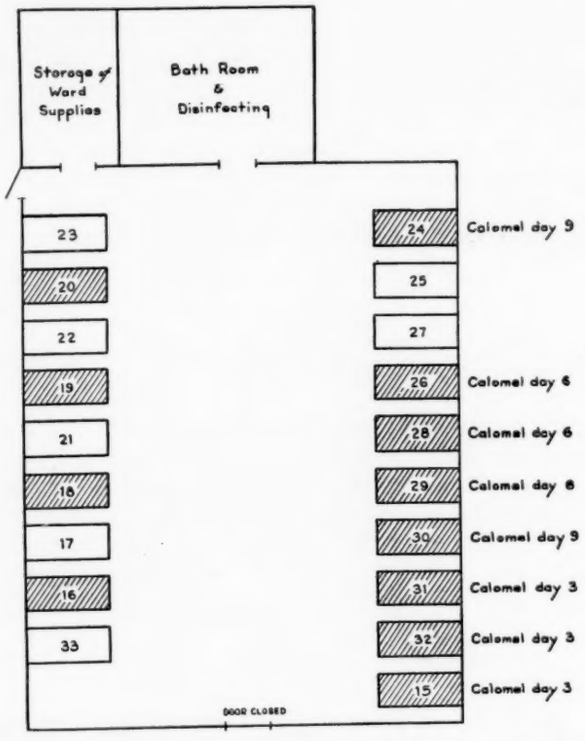

Fig. 4.—Ward B, hospital ward contact transmission trial group. Shaded areas, subjects fed type 1 SM virus; white areas, subjects fed no virus.

were physically disabled to a considerable extent, active play was prevented, and even those with normal motor ability did not demonstrate normal social behavior.

Contact was brought about by putting all of the children except two with hydrocephalus together on a plastic-covered mat for a three-hour "play" period daily from the day of virus feeding to 20 days thereafter. The cover

TABLE 4.—*Estimation of Transmission or Reception of Infection from Attenuated Virus*

Group A—Virus Fed (Donors)	Likelihood of Transmission
Subject 6	Great
4	Great
12	Moderate
2	Moderate
8	Slight
Group B—No Virus Fed (Recipients)	**Likelihood of Reception and Ingestion**
Subject 13	Great
9	Great
3	Moderate
1	Moderate
11	Slight
7	Slight
14	Very slight

of the mat was not allowed to become grossly soiled. It was washed with water but not disinfected at any time. Fecal spreading during the contact period was prevented by the early detection and diaper-changing of subjects who defecated during this time. The children moved about, played together, and used common toys insofar as their physical and mental disabilities permitted. The more active children were selected for virus feeding in the hope that they would move about and contact the less active subjects. This hope was only partially realized. Detailed notes were made on the behavior of the subjects during the contact period, and from these an estimate was made for each child of the likelihood of his having transmitted or received contamination. The transmission or reception of infection was estimated as shown in table 4. (For identification see figure 3, ward A.)

It was of interest that the number of contacts with donors made by recipients was determined mainly by specific selection of certain recipients by donors who used the very inactive children as play objects. Thus activity and motion on the part of a recipient did not necessarily insure frequent contact with a donor. Even the most negative of the recipients (subject 14) achieved at least eight definite skin-to-skin contacts with donors during 20 contact periods. Recipients high on the list, such as subject 13, achieved direct contacts between 5 and 10 times per period. The two with hydrocephalus, subject 10 who was fed virus and subject 5 who was kept as a contact, were placed together in a crib during the three-hour contact periods. Both of these subjects used their hands effectively, handled common toys, and touched each other frequently.

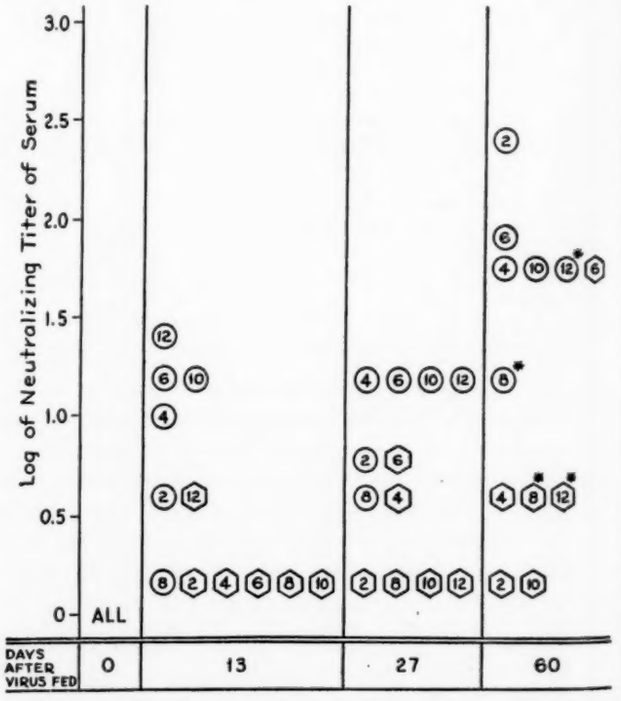

Fig. 5.—Antibodies against types 1 and 2 in the donor group (group 1) fed 200 plaque-forming particles of type 1 and 4.9 mouse paralytic doses of type 2. Numbers in circles, number of subject with antibodies against type 1; numbers in hexagon, number of subject with antibodies against type 2. Asterisks indicate 86 days after virus fed.

As indicated in table 3, all six donors excreted virus in their stools for varying lengths of time. Stools of two subjects already contained virus on the first day after its ingestion. (Stools of all children, collected prior to administration of the virus, had no cytopathogenic effect on monkey kidney epithelium grown in tissue culture.) One subject started to excrete virus on the 16th day after its administration. As shown in figure 5, all six donors

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developed antibodies against type 1, but only four did so against type 2. Moreover, type 2 antibody levels in serums of three of the four were of low order. This was caused by the interference between type 1 and 2 viruses, a phenomenon described previously [1b] and observed again in the course of this trial. As shown in table 3, three of the eight contacts who were placed on the mat became infected with type 1 virus. It may be interesting to note that the likelihood of contracting contact infec-

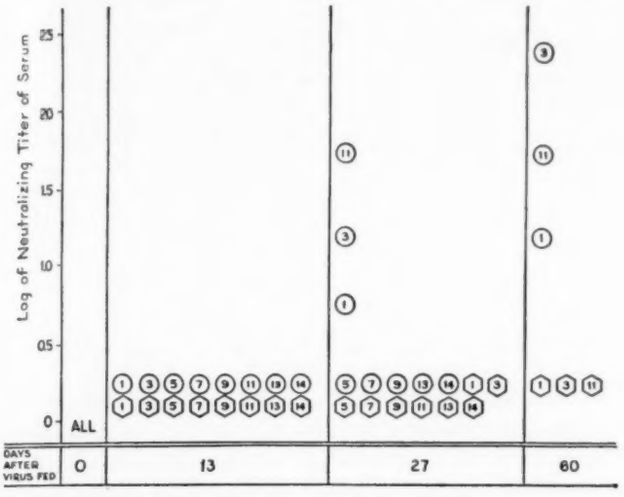

Fig. 6.—Antibodies against types 1 and 2 in contact group (group 2) fed no virus. Numbers in circles, number of subject with antibodies against type 1; numbers in hexagons, number of subject with antibodies against type 2.

tion had been considered only as "moderate" in subjects 1 and 3 and "slight" in subject 11. Subjects 9 and 13, who were classified as those with the greatest possibility of contact infection, failed to acquire alimentary infection.

In the case of subject 3, the contact infection must have occurred immediately, since virus was found in her stool on the fourth day after the six donors were fed. The other two contacts became infected later, as indicated by the first appearance of fecal virus on the 10th and 11th days respectively. None of the three contacts showed any signs of illness, and, as shown in figure 6, they were the only subjects of the eight in the group who developed type 1 antibodies by the 27th day after being placed in contact with the six donors. The remaining five contacts were kept under constant surveillance for 16 days after their separation from the donor group, a total of 36 days from first exposure. They did not excrete virus and did not develop antibodies (fig. 6). After this period they were fed type 1 and 2 viruses and promptly became intestinal carriers and developed antibodies.

It may be of interest to mention that there were nine nurses in contact with the 14 children, comprising groups 1 and 2 in ward A, who provided constant nursing care for their patients. As shown in table 5, seven of the nurses had no antibodies against type 1 at the start of the clinical trial, and two and one-half months later they still had no antibodies against type 1. One may deduce from these observations that the attenuated type 1 virus is not very contagious. The 3 to 8 ratio of infected contacts, supplemented by the results observed in the nurses, would seem to support this claim beyond question.

Another attempt to investigate the contagiousness of the attenuated strains was undertaken in ward B (fig. 1 and 4). The aim in this area was to approximate the degree of contact that might be expected in a hospital ward. In this case, 12 children were fed type 1 only. Eight of these received mild mercurous chloride (calomel) in an attempt to control the excretion of virus, and four were kept untreated as donors for seven children who had no antibodies against any of the three types of virus and who were placed in the same ward. The crib arrangement of this ward is shown in figure 4. It will be seen that the same general system of alternate cribs of virus-fed and contact subjects was employed as in ward A, except that the individuals who were to receive mercurous chloride later were grouped together in adjacent beds. The average distance between cribs was 3 ft., but several children were capable of moving their cribs and approaching those occupied by others. The two who did this most frequently were subjects 22 and 32.

Several children had a tendency to spread their feces about their immediate environment, and these children often badly soiled their own cribs and bedding. Children who most often manifested this tendency were a donor (subject 19) who did this almost daily, a contact (subject 22) who did this six times in 18 days, and another donor (subject 18) who did this two times in 18 days. Whenever this occurred, all "contaminated" bedding was changed and metal parts of the cribs were cleaned with Wescodyne.

Although an attempt was made to prevent direct contact between children in ward B, several "breaks" were observed. In one "break" a recipient (subject 22, fig. 4) reached into the crib occupied by a donor (subject 19, fig. 4) and handled a soiled diaper belonging to the latter, actually probably consuming a fragment of con-

TABLE 5.—*Absence of Evidence of Poliomyelitis Infection in Nurses Who Cared for Patients Fed Live, Attenuated Poliomyelitis Virus*

Nurses	Date of Bleeding	Day of the Trial	Presence of Antibodies Against		
			Type 1	Type 2	Type 3
1	4/3	− 1	0	0	+
	6/15	72	0	0	+
2	4/3	− 1	0	+	+
	6/15	72	0	+	+
3	4/3	− 1	+	0	+
	7/12	99	+	0	+
4	4/2	− 2	0	0	+
	6/15	72	0	0	+
5	4/3	− 1	+	0	+
	7/12	99	+	0	+
6	4/2	− 2	0	+	+
	7/4	91	0	+	+
7	4/5	1	0	+	+
	5/29	54	0	+	+
8	5/2	28	0	+	+
	5/29	54	0	+	+
9	5/2	28	0	0	0
	5/29	54	0	0	0

taminated feces. In the other "break," a donor (subject 16) placed his fingers in the mouth of a contact (subject 33). These same two children also were found to be exchanging a toy rabbit. How serious these "breaks" in isolation were is evidenced by the fact that the only two of the seven "recipients" who contracted alimentary infection with type 1 poliomyelitis virus were subjects 22 and 33, both involved, as shown above, in direct contact with virus-excreting donors, one of whom (subject 19)

was accustomed to spreading fecal material around himself. As indicated in table 6, all of the donors became intestinal carriers of type 1 virus and developed homotypic antibodies. The two infected contacts showed no signs of illness, remained intestinal carriers for a considerable length of time, and developed homotypic antibodies. (Characteristics of the type 1 virus isolated after either one or two passages through human intestinal tract will be the subject of a separate communication.)

Attempts to Suppress Alimentary Infection.—LoGrippo and others,[12] working with mouse poliomyelitis virus, observed that a mercurial compound had a suppressive effect upon virus-induced alimentary infection in mice. It seemed to be of interest to determine whether their findings were applicable to poliomyelitis virus infection in man, and particularly whether the duration of fecal excretion of attenuated strains would be shortened. Oral medication with three types of compounds was chosen: mild mercurous chloride because of the above

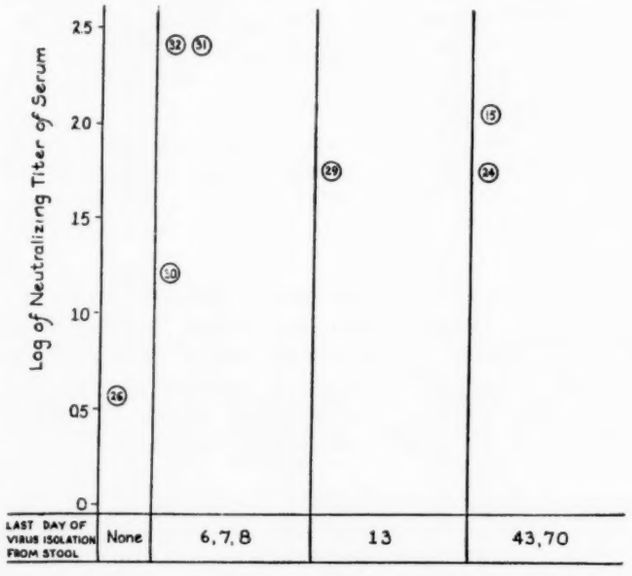

Fig. 7.—Duration of alimentary infection and development of antibodies against type 1 in subjects fed 200 plaque-forming particles of type 1. Numbers in circles, subject numbers. All subjects received mild mercurous chloride (calomel). Day of administration of virus is zero day.

work and the long history of application in human medicine; albumin tannate (Tannalbin) because of experimental evidence [13] of the antiviral effect of tannic acid; and diiodohydroxyquin (Diodoquin) because of its iodine content and possible antiviral effect. Mercurous chloride was given in a dosage of 1/10 grain (6 mg.) every half hour for four doses, then twice daily for eight days; albumin tannate in a dosage of 0.3 gm. six times daily for eight consecutive days; and diiodohyroxyquin in a dosage of 325 mg. four times daily to four children and twice daily to six children for eight consecutive days.

The results of the administration of these drugs to children who were excreting poliomyelitis virus at the time medication was started are shown in table 7. It should be pointed out that it was a very difficult task to evaluate the actual suppression of fecal excretion of the virus. Subjects who received no medication at all very often ceased excretion of the virus in a relatively short time after its ingestion. The criterion of drug effect was, of necessity, arbitrary and, therefore, criticism may be justified.

TABLE 6.—*Attempts to Prevent Direct Contact—Transmission of Attenuated Poliomyelitis Virus from Man to Man*

Groups and No. of Subjects in Group	No Pre-feeding Antibody to Types	Subject	Duration of Intestinal Carriage of Type 1	Antibody Response * After Virus Fed		
				13 Days	27 Days	60 Days
Donors † 4	1, 2	16	2-56	1.2	1.8	2.4
		18	1-56	1.2	1.8	2.4
		19	5-76	0.9	1.2	2.4
		20	5-24	0.3	2.4	1.8
Contacts 7	1, 2, 3	17	None	None	None	None
		21	None	None	None	None
		22	14-157	0.3	0.3	1.8
		23	None	None	None	None
		27	None	None	None	None
		25	None	None	None	None
		33	14-97 122-124	0.3	1.8	1.8

* Antibody titer expressed as common logarithms.
† 200 plaque-forming particles of SM (type 1) administered.

As shown in table 7, mercurous chloride seemed to exert a suppressive effect upon excretion of the virus. The results were equivocal, but it is our feeling that some effect on alimentary infection with type 1 virus was achieved. The action of albumin tannate was much less marked, and the effect of diiodohydroxyquin was nil. In several instances, listed under the "partial" column in the table, the apparent "disappearance" of the virus from stools was only temporary, lasting from four to seven days. Then the virus "reappeared" in the feces, often at a concentration equivalent to that observed before medication.

Administration of mercurous chloride sometimes was accompanied by side-effects, consisting, in order of frequency, of stomatitis, vomiting, and papular rash. The administration of albumin tannate and diiodohydroxyquin was almost without side-effects. Cessation of virus excretion in some of the children who received mercurous chloride permitted comparison of the duration of

TABLE 7.—*Attempts to Suppress by Medication Excretion of SM Strain (Type 1) of Poliomyelitis Virus in Stools*

Drug	No. of Subjects Treated	Treatment Started *	Side-Effect	Suppression of Viral Excretion		
				None	Partial	Complete
Mild mercurous chloride (calomel)	3	3	Present	..	1 (4) †	2
	1	6	Present	..	.....	1
	1	9	Present	1	.....	..
	8	20	Present	5	1 (4)	2
	5	26	Present	2	1 (4)	2
Albumin tannate (Tannalbin)	4	8	None	3	1 (4)	..
	3	44	.....	1	1 (7)	1
Diiodohydroxyquin (Diodoquin)	5	8	None	5	.....	..
	2	44	.....	2	.....	..

* Days after administration of virus.
† Figures in parentheses refer to the number of days of failure to recover the virus from stools.

intestinal carrier state with antibody response, as shown in figure 7. Not taking into consideration subject 26, who failed to excrete virus and who developed a very low antibody titer, one may conclude that the development and level of type 1 antibodies is in no way related to the actual duration of alimentary infection with the

12. LoGrippo, G. A.; Earle, D. P., Jr.; Graef, I., and Ward, R.: Effect of Mercurial Compound in Suppressing Intestinal Carriage of Theiler's Virus (TO) in Mice, Am. J. Hyg. **55**: 70, 1952.

13. Sabin, A. B.; Olitsky, P. K., and Cox, H. R.: Protective Action of Certain Chemicals Against Infection of Monkeys with Nasally Instilled Poliomyelitis Virus, J. Exper. Med. **63**: 877, 1936.

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SM strain, since similar antibody levels were noted in subjects 24 and 15, who excreted the virus for 43 and 70 days, and in subjects 31 and 32, who ceased to excrete it on the sixth and eighth day after its ingestion.

Simultaneous Administration of Attenuated Viruses and Immune Serum Globulin.—Although the results of mass administration of immune serum globulin to human subjects during the epidemic of 1953 were not very encouraging,[14] its protective value against paralytic infection in monkeys had been definitely ascertained by Bodian.[15] It was of interest to determine the effect of immune globulin injected at the time of ingestion of attenuated viruses. Four subjects (5, 17, 7, and 21) who had been used as contacts in the trial described above and two subjects (28 and 52) who had failed to become infected with the SM virus, either because of regurgitation (subject 28) or because of having received virus beyond its infectivity end-point, were inoculated intramuscularly with immune serum globulin, 0.15 ml. per pound of body weight (table 8). At the same time, all six received 200 plaque-forming particles of type 1 virus and four (subjects 5, 7, 17, and 21) of the six were also fed $10^{4.6}$ P. $D._{50}$ of type 2. Five other subjects who also were previously used as "contacts," who had developed no antibodies and had not showed intestinal carriage of the virus, received the two viruses but no immune serum globulin. The results of the trial seem to indicate that the administration of immune serum globulin has no effect whatsoever on the duration of the intestinal carrier state or on antibody development after the feeding of live viruses. None of the 11 subjects was found to excrete type 2 virus, and 2—one in each group—failed to excrete type 1. This could be attributed to interference between types 1 and 2 and thus would have no relation to the use of immune serum globulin.

The lack of influence of immune serum globulin upon the actual level of antibodies developed as the result of virus administration is illustrated in figure 8 for type 1 antibodies and figure 9 for type 2 antibodies. Once more it was practically impossible to distinguish between subjects who received globulin and those who did not. The failure of two individuals to develop type 2 antibodies may again be ascribed to interference.

Reexposure to Alimentary Infection with Living Attenuated Virus of Individuals Already Immunized with the Same Homotype.—The results of reexposure to a viral homotype of a person who already has antibodies remain controversial, principally because of a dearth of quantitative observations. In the preliminary studies re-

TABLE 8.—*Effect of Immune Serum Globulin on Carrier Rate in Subjects Fed Type 1 and Type 2 Simultaneously* *

Group Given	Subject	No Prefeeding Antibody to Virus Types	Duration of Carrier State (Type 1),† No. of Days	Antibody Response	
				Type 1	Type 2
Immune Globulin ‡	5	1, 2, 3	1-23; 29-58; 64-69	+	+
	7	1, 2, 3	4-111	+	+
	17	1, 2, 3	None	−	+
	21	1, 2, 3	2-38; 46-52	+	−
	28 §	1, 2	3-12; 16-20	+	..
	52 §	1	1-28; 39-41; 53-63	+	..
Nothing	13	1, 2, 3	3-58; 64-69	+	+
	14	1, 2, 3	11, 23-58; 49-52	+	−
	23	1, 2, 3	1-52	+	+
	27	1, 2, 3	1-90	+	+
	25	1, 2, 3	None	−	+

* 200 plaque-forming particles of type 1 (SM) and $10^{4.6}$ mouse paralytic doses of type 2 (TN).
† No type 2 virus was excreted.
‡ 0.15 ml. per pound of body weight, intramuscularly.
§ Received type 1 only.

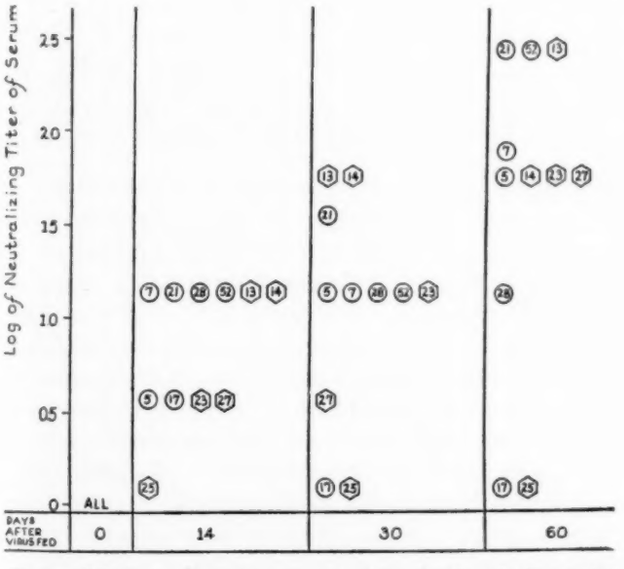

Fig. 8.—Effect of gamma globulin on development of antibodies against type 1 in subjects fed 200 plaque-forming particles of type 1. Numbers in circles, number of subject receiving gamma globulin; numbers in hexagon, number of subject not receiving gamma globulin.

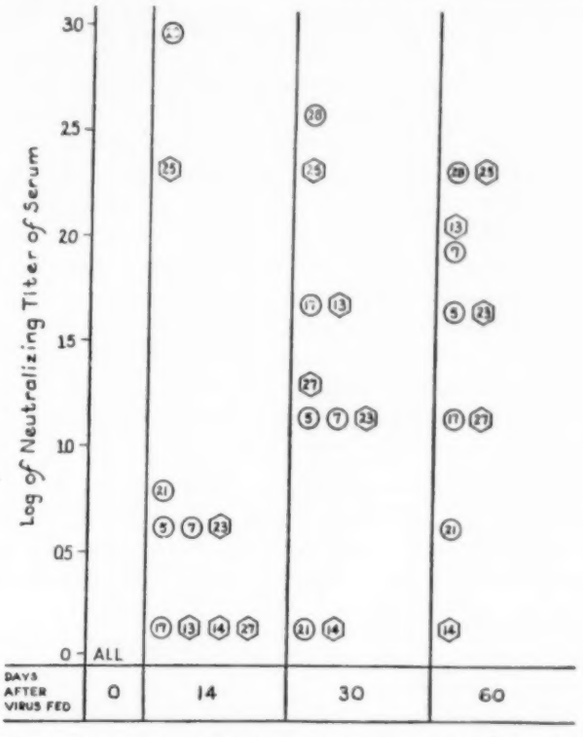

Fig. 9.—Effect of gamma globulin on development of antibodies against type 2 in subjects fed 4.6 mouse paralytic doses of type 2. Numbers in circles, number of subject given gamma globulin; numbers in hexagons, number of subject not given gamma globulin.

14. Evaluation of Gamma Globulin in Prophylaxis of Paralytic Poliomyelitis in 1953: Summary of the Report of the National Advisory Committee for Evaluation of Gamma Globulin, Special Article, J. A. M. A. **154**: 1086 (March 27) 1954.

15. Bodian, D.: Experimental Studies on Passive Immunization Against Poliomyelitis: Prophylactic Effect of Human Gamma Globulin on Paralytic Poliomyelitis in Cynomologous Monkeys After Virus Feeding, Am. J. Hyg. **56**: 78, 1952.

lated to this problem conducted four years ago,[1a] 12 subjects who developed type 2 antibodies as the result of virus feeding were refed the same strain of virus after an interval of two to three months. The carrier state was again established in 2 of the 12. No significant rise in homotypic antibody levels was observed.

TABLE 9.—*Effect of Refeeding* Type 2 Virus to Human Subjects Three Years After Original Feeding*

Group	Status	No. of Subjects	No. Excreting Virus	Ratio of Antibody Response
14	Fed before	19	10	16/19 †
13	Control	3	3	3/3 ‡

* Amount of TN virus fed approximated 100 human infectious doses.
† Represents booster response.
‡ Represents primary response.

From another clinical trial conducted three years ago,[6] 19 subjects were selected who had developed type 2 antibodies after oral administration of the TN strain at that time. In the present trial they were refed the same preparation of virus, which had been kept frozen during the interval. The preparation represented an infected cotton rat brain and spinal cord suspension.[16] This, in contrast to the mouse-adapted substrain of TN virus reported in the foregoing (table 2), can be recovered from excreta more easily, and the carrier state can be determined in a more accurate way.[16] In addition to

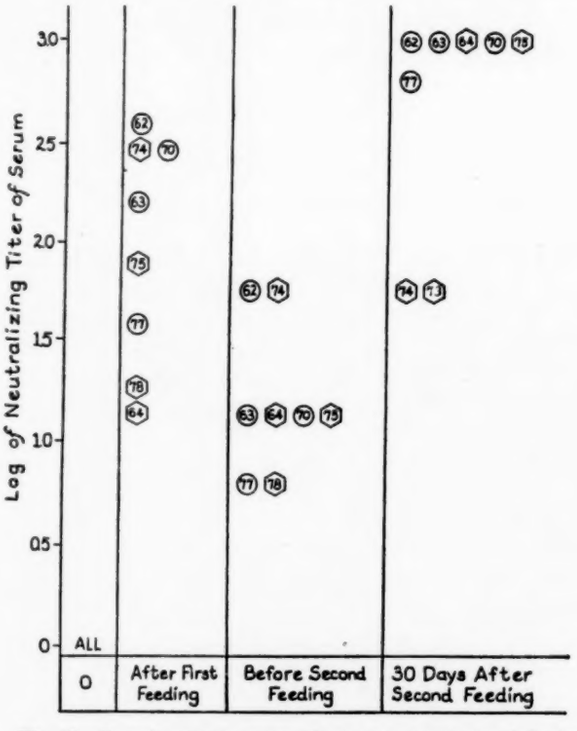

Fig. 10.—Type 2 antibody levels of subjects reexposed to infection with TN strain. Dose fed was $10^{4.7}$ mouse paralytic doses of TN (type 2), equivalent to 100 human infectious doses. Numbers in circles, number of subject who did excrete virus; numbers in hexagons, number of subject who did not excrete virus.

these 19 subjects (table 9), 3 individuals who had never been exposed to virus before and who had no antibodies against type 2 received the same virus preparation. Since the same strain was used for titration purposes in man (table 2), it was possible to calculate that the inoculum consisted of approximately 100 human infectious doses.

As shown in table 9, the three previously nonexposed subjects excreted virus in their stools and developed type 2 antibodies. Ten of the 19 reexposed individuals excreted virus again on one or more occasions. As shown in table 10, the excretion of the TN strain in the 3 "control" and the 10 "reexposed" subjects was of sporadic nature, characteristic of infection with this type of virus. In two control and four reexposed subjects, no virus could be isolated except by the use of the blind-passage technique. Stools of the remaining nine reexposed subjects were found to be free from virus during a "collection" period of 30 days. With three exceptions, ingestion of the virus for the second time resulted in a booster effect on the antibody levels.

The appearance of virus in stools of reexposed subjects was in no way related to the existing measurable levels of antibodies. This is best shown in figure 10, which illustrates serum antibody levels of four pairs of subjects reexposed to virus. It may be observed that only

TABLE 10.—*Virus Excretion of TN Strain in Subjects Reexposed to Virus*

Group	Subject	Virus Excretion Days After Feeding: Direct Inoculation	Virus Excretion Days After Feeding: Blind Passage
Control	42	0	12
	57	0	9-12
	58	7-27	28-31
Reexposure *	60	0	12-14
	61	4-24	26-28
	62	9	4-7; 12; 13
	63	0	11-16
	66	0	23-28
	67	8-30	.....
	68	0	8-11
	70	5-28	.....
	71	6-13	14-17
	77	7-11	14

* Excreta of reexposed subjects not mentioned in this table failed to yield virus by either direct isolation or blind-passage technique.

one subject of each pair excreted virus, although the antibody levels were identical for each pair at the time of refeeding. It should be pointed out, however, that the antibody titers ranged from $10^{0.6}$ to $10^{1.8}$, and it is impossible to predict what the results of such a trial would have been had the virus been administered for the second time to individuals with much higher homotypic antibody titers. However, since the amount of virus fed these individuals was not very large—representing only approximately 100 human infectious doses—it may be deduced that reinfection of the human intestinal tract with type 2 virus may occur in subjects whose antibody titer is as high as 1:64.

Interference.—Data obtained in previous trials indicated that "mixed" feeding with types 1 and 2 often resulted in interference, the type 1 virus apparently gaining the "upper hand."[17] These results made it imperative to feed much larger doses of type 2 virus in a mixture with type 1. In the present trial the same procedure was followed, again resulting in interference between the two types, although the type 1 strain was not always dominant.

16. Footnotes 1*a* and 6.
17. Footnote 1*b* and *c*.

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Data pertinent to this problem are summarized in table 11. Six subjects, forming group 1, became type 1 (SM) intestinal carriers and developed type 1 antibodies, but only four also developed antibodies against type 2.

TABLE 11.—*Reciprocal Interference Between Type 1 and Type 2 in Intestinal Tract of Man*

Group	No Prefeeding Antibody to Types	Amounts of Virus Fed *		Ratio of Subjects Fed Who Developed Antibody		Intestinal Carriage	
		Type 1, P. F. P.†	Type 2, P. D.$_{50}$ ‡	Type 1	Type 2	Type 1	Type 2
1 §	1, 2	2.3	4.9	6/6	4/6	6/6	0/6
16 §‖	1, 2, 3	2.3	4.6	4/5	4/5	4/5	0/5
17 §	1, 2, 3	2.3	4.6	4/5	4/5	4/5	0/5
4	1, 2	2.3	None	4/4	...	4/4	...
3a	2	None	4.6	...	3/3	...	0/3

* Expressed as common logarithms.
† P. F. P., plaque forming particles.
‡ P. D.$_{50}$, mouse paralytic doses.
§ Simultaneous administration of the two viruses: SM in capsule, TN in milk.
‖ Given injection of immune serum globulin.

Thus, type 2 (TN) infection was suppressed in two subjects fed the mixture of viruses. Five subjects, who formed group 16, received one injection of immune serum globulin at the time of virus administration. Four of the five became intestinal carriers of type 1 and developed type 1 antibodies. The same ratio of antibody response was observed in relation to type 2. Thus, in a group of five subjects fed the two viruses simultaneously, one failed to develop type 1 antibodies and another developed no antibodies against type 2. The same reaction was observed in subjects forming group 17, who were treated in the same way as group 16 except that they did not receive immune serum globulin. Evidence to support interference as the cause of the above results comes from data obtained in groups 4 and 3A; the subjects in these groups received either SM or TN viruses alone. All individuals developed homotypic antibodies promptly.

The interference effect of type 1 virus was overcome in a previous trial when type 2 was administered five days before type 1.[1c] It seemed to be of interest to determine if alimentary infection with TN (type 2) virus could be established in subjects who had received type 1 virus some time before, some of whom were still excreting virus. Four subjects were chosen for this study; their histories are shown in table 12. None of them had antibodies against types 1 and 2 when the trial was started (data condensed from table 1). They were first fed the SM (type 1) strain, and, as indicated in table 12, all became intestinal carriers and all developed homotypic, but not heterotypic, antibodies. On the 72nd day after administration of the SM strain, when two (subjects 19 and 47) of the four were still excreting type 1 virus in amounts equivalent to $10^{3.25}$ T. C. D.$_{50}$ per gram of feces, the type 2 strain was given orally in milk in a dose that had been used in other groups where interference was observed. All four subjects developed antibodies against type 2 virus. One individual failed to excrete type 2 virus, but the remaining three did excrete it. Of more than usual interest is the observation on alimentary infection of subjects 19 and 47. Both continued to excrete type 1 virus for five days after administration of TN (type 2) virus. From then on, only type 2 virus appeared in the feces of subject 47, though it is quite probable that both viruses were present in the six to eight day collections, since the isolated agent was not neutralized by either type 1 or type 2 antiserums. Type 2 virus appeared in feces of subject 19 only once during the 16 to 22 day period after its administration.

These results would seem to indicate that interference will result when the two viruses are administered simultaneously, apparently competing to establish a "foothold" in the alimentary tract, but that, if one virus is given ahead of the other and is already established in the human intestinal tract at the time of administration of the other type, there is no interference. These observations are based on meager statistical evidence and would require confirmation in a larger number of subjects. Unless evidence to the contrary is obtained, it would appear justifiable at this time to recommend administration of the two strains a month or so apart. In all probability, interference would not occur.

TABLE 12.—*Oral Administration of TN Strain to Subjects Fed SM Virus Seventy-Two Days Before*

Subject	1st Feeding (Type 1)				2nd Feeding (Type 2)									
	Amount Fed, P. F. P.*†	Duration of Alimentary Infection, Days	Antibody Response, Type 1		Amount Fed, P. D.$_{50}$ *§	Identity of Excreted Virus After Type 2 Administration							Antibody Response, Type 2	
			Time ‡	Titer *		1 Day	2-5 Days	6-8 Days	9-12 Days	13-15 Days	16-22 Days	23 Days	Time ‖	Titer *
16	2.3	2-56	60	2.4	4.9	None							14	1.8
18	2.3	1-56	60	2.4	4.9	0	2	2	2	2	2	0	14	1.8
19	2.3	5-77	60	2.4	4.9	1	1	0	0	0	2	0	14	1.8
47	1.3	3-75	60	2.4	4.9	1	1	?	2	0	2	2	14	1.2

* Expressed as common logarithms. † P. F. P., plaque-forming particles. ‡ Days after administration of type 1. § P. D.$_{50}$, mouse paralytic doses.
‖ Days after administration of type 2.

Comment

Inclusive of the current trial, 150 nonimmune subjects have received the TN (type 2) strain and 75 the SM (type 1) strain for immunization purposes. None of the subjects suffered any ill-effects attributable to the ingestion of living poliomyelitis virus. Although, because of the mental status of some of the patients, it is conceivable that some subjective symptoms following administration of virus may have passed unnoticed, it is unlikely that this occurred, since complaints were promptly voiced and recorded in cases of accompanying intercurrent infections.

The characteristic previously observed [17] behavior of the two types of virus in human subjects has been confirmed in the present trial. The noncytopathogenic TN type 2 virus was encountered only sporadically, and then

only at very low concentrations, in excreta of subjects fed the virus. Conversely, if one disregards the cases of interference, the SM type 1 virus was recovered from stools of every subject who ingested it. The duration of alimentary infection with the SM strain was, in general, unpredictable and appeared to be in no way related to the promptness of development and concentration of homotypic antibodies. The rate of alimentary infection and antibody development was not influenced by the simultaneous administration of immune serum globulin, a fact suspected before [2] but now definitely confirmed. The fact that one child (subject 8, table 3) excreted the type 1 virus only between the sixth and ninth day after its administration and another child (subject 6, table 3) between the 1st and 104th day of the trial made it difficult to evaluate the influence of any drug that could be used for the suppression of viral excretion from the alimentary tract. A drug that would effectively control virus excretion is yet to be found. Mild mercurous chloride, used in the present trial, seemed to show some suppressive activity, but, without any apparent reason, it seemed to be effective only in certain cases, and some of the side-effects accompanying its administration were not of trifling character.

The transmission of the attenuated type 1 strain of virus from child to child occurred in 5 out of 15 contacts. These children (three in ward A and two in ward B) who became infected were in direct, and often intimate, contact with the virus-fed donors. None of the remaining five children of ward B, who were not observed to have direct contact with the four donors, became infected. Only three of eight children who had close contact with six donors in ward A acquired infection. These records, supplemented by the results observed in the nursing personnel (table 5), would indicate that the SM virus is not very contagious. It should be mentioned, however, that the virus was fed to the group of future "donors" in a capsule, bypassing the throat region and leaving only the lower end of the alimentary canal as possible source of contamination. If the elimination of multiplication in the throat region conditioned the low degree of transmissibility of the virus, then the arguments for administration of the virus in capsule form are very strong indeed.

A question may be raised relative to the correlation of the low degree of contagiousness of the type 1 virus if 2 plaque-forming particles of the same SM strain when ingested were found to be infectious for intestinal mucosa in two out of three children (table 1). It is certain that, even though the excretion is of constant character, the amount of SM virus excreted by a child per day per total fecal material produced is not very large, and, furthermore, fecal virus is not as readily "available" for transmission as, for instance, if it were lodged in the throat and secreted in saliva; i. e., manual contact with the anal area is much less frequent than with the oral. Whether the development of other variants of virus can prevent the high frequency of SM virus excretion from the human intestinal tract still remains to be seen. In contrast to the highly cytopathogenic SM virus, the noncytopathogenic TN strain has a very low rate of multiplication in the human intestinal tract, as indicated by its sporadic appearance and very low concentrations in stools. Do the noncytopathogenic properties of the virus determine its behavior in the human host? Development of a noncytopathogenic type 1 would provide a welcome opportunity to test, at last, this hypothesis. Since the low degree of contagion applies at present only to attenuated—through prolonged and exhaustive laboratory manipulation—forms of virus, generalization on the basis of these findings may be inadvisable. It is quite clear, however, that, when principles of simple personal hygiene are practiced, the attenuated SM virus, after its administration in a capsule, may be completely prevented from passing from one subject to another.

The idea of live virus immunization can be advocated only if all the subjects who receive the virus respond with antibody formation. Judged from this point of view, the present trial seemed to justify a certain amount of optimism. Disregarding the interference phenomenon, which apparently can be bypassed, as indicated by the result of one trial, all subjects fed either of the viruses developed homotypic antibodies. The virus suspensions or "viral" capsules, however, have to be swallowed: one or two patients who regurgitated the virus immediately after its administration failed to respond. That presence of serum antibodies is no prevention against establishment of alimentary infection with homotypic virus was known before.[18] The results of the present trial confirm and amplify these findings.

The future of live virus immunization against poliomyelitis is bright from the point of view of scientific developments. The number of immunizations of nonimmune individuals without accident has given increased confidence in the use of live, attenuated strains of strictly defined characteristics. With this slow, but steady and cautious, progress in research, it is hoped that one day the living, attenuated viruses will find their proper place in the line of combat against poliomyelitis.

Summary

Inclusive of the current trial, 150 nonimmune subjects have received the TN (type 2) strain and 75 the SM (type 1) strain of poliomyelitis virus for immunization purposes. None of the subjects suffered any ill-effect that could have been attributed to the ingestion of living poliomyelitis virus, and all developed antibodies. The type 1 (SM) strain was excreted by every individual; the type 2 (TN) strain was rarely excreted. Transmission of the attenuated type 1 strain from child to child occurred in 5 out of 15 contacts under the most intimate contact conditions established for the experiment. Attempts to suppress viral excretion in stools by the use of drugs met with little success. Administration of gamma globulin at the time of virus feeding had no effect on antibody response. It was confirmed that the presence of serum antibodies does not prevent the establishment of alimentary infection with homotypic virus in certain subjects.

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CLINICAL NOTES

DEVELOPMENT OF ANTIBIOTIC RESISTANCE BY BACTERIA

EFFECT OF SERIAL SUBCULTURE IN ANTIBIOTIC MIXTURES

Norman Molomut, Ph.D.
Leon J. Warshaw, M.D.
and
Elizabeth M. Gross, B.S., Port Washington, N. Y.

The increasing incidence of antibiotic-resistant strains of micro-organisms and the corresponding increase of infections that fail to respond to treatment with any single antibiotic, even when large doses are used, has caused much concern in many quarters.[1] The intensified search for new and more potent antibiotic agents provides some comfort, although it is evident that pathogenic micro-organisms will develop resistance to each new drug as it is introduced into general use.

Physicians confronted by a seriously ill patient whose infection seems to defy first one, then another, and occasionally even a third antibiotic can rarely afford the time to try all of the currently available antibacterial drugs, much less wait for the discovery of newer ones. Some have used larger and larger doses of a particular drug, but with only a rare success. Others have resorted to the simultaneous administration of two or more antibiotics. In a previous paper,[2] organisms resistant clinically and in vitro to ordinary doses of single antibiotic agents were shown to be inhibited in vitro by combinations of two or more antibiotics, even though each was present in concentrations far lower than those found ineffective when used singly. Despite some reports of antagonism when certain antibiotic agents are used in combination,[3] clinical experience has been gratifyingly successful. As a result, the empirical use of antibiotic combinations has become increasingly popular. It seemed proper, therefore, to investigate the ability of micro-organisms to acquire resistance to antibiotic combinations.

Method

All organisms used in this study were isolated from patients with persistent infections. Each organism was found to be resistant in vitro to the individual antibiotics in the following concentrations: penicillin 1 unit per milliliter, chlortetracycline (aureomycin) 1 mcg. per milliliter, bacitracin 10 units per milliliter, neomycin 10 units per milliliter, streptomycin 10 mcg. per milliliter, triple sulfonamides 30 mcg. per milliliter (10 mcg. per milliliter each of sulfadiazine, sulfamerazine, and sulfamethazine). Neisseria catarrhalis and hemolytic Streptococcus were selected as representative of the more virulent and parasitic types of micro-organisms usually found in acute severe infections. This group, designated as "obligate parasites," generally displays a narrow range of adaptability to alterations in enviroment. Proteus vulgaris, a nonhemolytic Micrococcus (Staphylococcus) pyogenes var. aureus, and a beta-hemolytic M. pyogenes var. aureus represented those more saprophytic organisms usually associated with relatively indolent and chronic infections. This group tolerates considerable variations in environment.

Eleven combinations of antibiotics were employed (table 1). The mixtures were made up in sterile yeast extract broth containing a concentration of 100 mcg. per milliliter or 100 units per milliliter of each antibiotic with the exception of the triple sulfonamides, which were used in a total concentration of 500 mcg. per milliliter. Fresh solutions were prepared every two weeks and stored at –30 C until used. For each mixture, five sets of 15 tubes representing a serial dilution from 100 mcg. or units per milliliter were prepared (table 2). Each of the five organisms was inoculated into every tube in one set. The inoculum for each series was taken from the previous serial dilution test, using the first tube showing growth. To keep the inoculum as uniform as possible, the growth was measured turbidimetrically and the culture diluted with sterile broth to a constant arbitrary concentration. The inoculum volume was 0.1 ml. Thus each organism was grown in serial subculture continuously in the presence of each of the 11 antibiotic combinations.

Suitable controls for organism viability in broth without antibiotics, for medium sterility and for pipetting procedure, were run for each serial dilution series. In addition, with every transfer an inoculum was plated out for study of colonial morphology, hemolytic characteristics, and smear for gram stain in order to check the purity of the culture. No instance of contamination was encountered. The entire procedure was repeated twice a week until a total of 50 serial subcultures of each organism in each of the 11 antibiotic mixtures was completed or until growth appeared in the first tube (100 mcg. or units per milliliter) in at least five successive transfers. In such instances, resistance acquired by that organism to the particular antibiotic mixture was assumed to be complete, and further subculture was discontinued.

Results

In evaluating the results of this study (table 1) it must be remembered that the particular micro-organisms employed were selected because they had proved resistant to each of the antibacterial agents when used singly. Exposing them to combinations of the same antibiotics resulted in instances of both synergism and antagonism. The hemolytic M. pyogenes var. aureus, for example, was able initially to resist the combinations of chlortetracycline and penicillin and chlortetracycline and bacitracin in concentrations of 3 units or micrograms per milliliter and 2 units or micrograms per milliliter respectively. Yet,

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when chlortetracycline, penicillin, and bacitracin were combined, 0.5 units or micrograms per milliliter was the upper limit of resistance. The N. catarrhalis, on the other hand, demonstrated exactly the opposite behavior. Against chlortetracycline and penicillin and chlortetracycline and bacitracin, its resistance stopped at concentrations of 0.06 units or micrograms per milliliter. The combination of chlortetracycline, penicillin, and bacitracin was effective only in concentrations in excess of 2 units or micrograms per milliliter.

Thus the combinations of chlortetracycline and penicillin and chlortetracycline and bacitracin were antagonistic in the case of the hemolytic M. pyogenes var. aureus and synergistic against the N. catarrhalis. The combination of all three drugs, however, demonstrated synergism against the hemolytic M. pyogenes var. aureus and antagonism against the N. catarrhalis. It is clear, therefore, that the effectiveness of combinations of two or more antibiotics shows considerable variation depending upon the individual characteristics of the particular organism involved.

These data permit the generalization that organisms classified as "obligate parasites" are more readily inhibited by smaller doses of combined antibiotics. Furthermore, it is apparent that, while some resistance to the antibiotic combinations is acquired by the "obligate parasites," it appears rather slowly and reaches a ceiling usually well within the range of antibiotic concentrations attainable by use of ordinary clinical doses. The demonstration that the "saprophytic" organisms rapidly become resistant to the relatively larger doses of the antibiotic combinations is a cause for concern. It would seem wise therefore to treat such infections initially with large doses of antibiotic mixtures to eliminate the organisms before they can develop resistance. Furthermore, the isolation of an infecting organism and assay of its sensitivity to antibiotics should be repeated at frequent intervals in each instance of prolonged infection to detect the rate of development of resistance. This procedure will also permit the detection of secondary invaders or instances of "superinfection." Finally, these data confirm the validity of the oft-repeated but seldom-heeded injunction against the indiscriminate use of antibiotic drugs.

Summary and Conclusions

The capacity of bacteria to develop resistance to antibiotic combinations was studied by the serial subculture of five organisms isolated from clinical cases and shown to be resistant to single antibiotics in mediums containing serial dilutions of 11 different antibiotic mixtures. Organisms representative of the "obligate parasites" were shown to be initially sensitive to the combinations of antibiotics. Their resistance to these drugs developed slowly and reached a ceiling at concentrations well within the range attainable by routine therapy. The "saprophytic" organisms were initially less sensitive to the antibiotic combinations and rapidly acquired the ability to grow in the presence of relatively high concentrations of these drugs. The data suggest the advisability of the initial use of high doses of combinations of antibiotic drugs in cases of prolonged infection in order to eliminate the offending organism before it can acquire resistance. They also emphasize the importance of repeating at frequent intervals in such cases the isolation of the infecting organism and retesting its sensitivity to the antibiotic drugs being employed.

16 Sintsink Dr. E. (Dr. Molomut).

TABLE 1.—*Effect of Serial Subculture in Antibiotic Mixtures on Development of Antibiotic Resistance by Bacteria*

Antibiotic Mixture	Neisseria Catarrhalis			Streptococcus			Hemolytic Micrococcus Pyogenes Var. Aureus			Proteus Organisms			Micrococcus		
	A*	B	C	A	B	C	A	B	C	A	B	C	A	B	C
Chlortetracycline-penicillin	0.06	0.5	21	0.12	2.0	34	3.0	10.0	33	3.0	100.0	5†	3.0	50.0	12
Chlortetracycline-bacitracin	0.06	1.0	27	0.25	5.0	33	2.0	10.0	37	5.0	50.0	4	2.0	100.0	20
Chlortetracycline-neomycin	0.12	10.0	33	0.12	1.0	31	30.0	100.0	4†	1.0	50.0	17	10.0	100.0	21†
Chlortetracycline-streptomycin	0.12	2.0	35	0.06	5.0	37	5.0	50.0	11	0.5	50.0	19	2.0	50.0	8
Chlortetracycline-penicillin-bacitracin	2.0	100.0	21†	0.03	2.0	33	0.5	10.0	23	0.03	2.0	33	1.0	100.0	27†
Chlortetracycline-penicillin-neomycin	0.06	0.5	29	0.12	0.12	1	0.5	10.0	28	2.0	100.0	31†	0.5	100.0	25†
Chlortetracycline-penicillin-streptomycin	0.06	0.25	23	0.12	0.5	15	2.0	5.0	29	5.0	100.0	14†	0.5	100.0	14†
Chlortetracycline-bacitracin-neomycin	0.06	2.0	25	0.12	1.0	25	2.0	5.0	37	0.5	50.0	27	0.5	100.0	31†
Chlortetracycline-streptomycin-neomycin	0.06	5.0	35	0.25	2.0	27	2.0	100.0	12†	1.0	50.0	22	0.25	50.0	22
Chlortetracycline-streptomycin-bacitracin	0.06	1.0	35	0.015	5.0	31	0.5	100.0	23†	0.5	50.0	15	0.12	50.0	23
Chlortetracycline-triple sulfonamides	0.12	100.0	29†	0.12	50.0	12	20.0	100.0	4†	2.0	100.0	9†	30.0	100.0	2†

* A, initial "resistance" (i. e., minimum concentration of antibiotics inhibiting bacterial growth), mcg. or units/ml.; B, peak "resistance," mcg. or units/ml.; C, subculture generation demonstrating peak "resistance."

† Resistance assumed to be "complete"; further subculture discontinued.

TABLE 2.—*Sample Experiment with Proteus Organisms and Penicillin, Neomycin, and Chlortetracycline**

	Tube No.														
	1	2	3	4	5†	6	7	8	9	10	11	12	13	14	15
Antibiotic concentration, mcg. or units/ml.	100	50	30	20	10	5	2	1.5	1.0	0.5	0.25	0.12	0.06	0.03	0.015
Bacterial (growth graded 0 to 4+)	0	0	0	0	2+	4+	4+	4+	4+	4+	4+	4+	4+	4+	4+

* Subculture generation 20.

† Organisms from tube 5 studied by gram-stained smear and plated out on blood agar for study of colony morphology and to check the purity of the culture. Growth in tube 5 was quantitated turbidimetrically and diluted with sterile broth to the arbitrary concentration used for inoculation. 0.1 ml. of the diluted culture was inoculated into each of the 15 tubes used for study of subculture generation 21.

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COUNCIL ON FOODS AND NUTRITION

Report to the Council

The following report has been prepared at the request of the Council on Foods and Nutrition.

EUGENE H. STEVENSON, M.S.
Acting Secretary.

CLINICAL AND NUTRITIONAL ASPECTS OF LIPOTROPIC AGENTS

WITH SPECIAL REFERENCE TO THEIR ROLE IN THE PATHOGENESIS AND TREATMENT OF FATTY CIRRHOSIS OF THE LIVER

George J. Gabuzda, M.D., Cleveland

Some clinical and nutritional aspects of the lipotropic factors, choline and methionine, are discussed in this paper. Clinical investigations are emphasized, but discussions of work with experimental animals that provide background or that have special implications for future clinical investigations are included in the appropriate sections. To provide perspective and orientation, the biochemistry and metabolism of lipotropic factors in normal man and in experimental animals are briefly outlined. Recent progress and trends in clinical investigations relating to choline and methionine are summarized. Finally, the present status of the therapeutic usefulness of these agents in fatty cirrhosis is evaluated on the basis of available data.

Definition

Lipotropic is a term applied to dietary factors that prevent the accumulation of abnormally large quantities of fat in certain animal organs. This designation originally referred to fat deposition in the liver [1] and in the kidneys.[2] More recently it has been proposed that the term lipotropic be extended to include factors that prevent the accumulation of lipid in other locations, specifically in the heart and in blood vessels.[3] Since its introduction, the term lipotropic has been used in reference to a variety of materials with the ability of preventing the accumulation or effecting the mobilization of fat from body organs. These range from complex materials such as proteins, lecithins, and lipocaic to substances such as choline, methionine, and vitamins. The term lipotropic then, by usage at least, is not specific regarding the factor that it characterizes nor the organ that is affected. This does not imply that the alterations that result after dietary deficiency of lipotropic factors and that lead to the abnormal accumulation of fat in tissues may not rest on common ground. Nor does it imply that the factors that display lipotropic activity may not circulate in common biochemical systems.

From the Department of Medicine, Western Reserve University School of Medicine and City Hospital.

Because of space limitations the bibliographic references have been omitted from THE JOURNAL and will appear in the author's reprints.

Historical Data

About 30 years ago the observation was made that fatty livers and subsequent fibrosis developed in depancreatized dogs even if they were maintained on a regimen of insulin.[4] Later studies revealed that this fatty liver was attributable to lack of external pancreatic enzymes and failure of digestion of protein, since the liver pathology was not affected by the feeding of whole protein but was reversed by whole pancreas or hydrolyzed protein given orally.[5] In 1932 it was reported that crude egg yolk lecithin protected pancreatectomized dogs from the development of fatty livers.[6] It was hypothesized that lecithin provided phospholipids, which were concerned with fat transport. Lecithin also protected rats on low-protein, high-fat diets from the development of fatty livers.[7] The active constituent of lecithin was identified as choline, since choline was also effective in preventing the development of fatty livers that were produced in rats by dietary means or that occurred in depancreatized dogs maintained on a regimen of insulin.[8] As the importance of protein became apparent in protecting animals from the development of fatty liver and cirrhosis, investigations turned to the factor in protein that was responsible for this protective action. The result of these inquiries indicated that, of the amino acids studied, only methionine exerted a potent lipotropic effect.[9]

The relationship between choline and methionine was clarified by du Vigneaud and associates, who showed by animal studies that the methyl group of methionine could be used for choline synthesis.[10] This work, in conjunction with the demonstration that in some animal species dietary methionine could be replaced by homocystine and an adequate source of methyl groups, served as the origin of the transmethylation theory in relation to the synthesis of choline from methionine. Studies utilizing heavy water indicated that methyl groups could be synthesized to some extent by intact animals.[11] Subsequent work with germ-free rats demonstrated the synthesis of methyl groups from deuterium oxide, indicating that the in vivo synthesis of methyl groups was not dependent upon the organisms in the gastrointestinal tract.[12] The background was thus established for the recent interest in the relation of factors concerned with the metabolism of single carbon units or methyl groups to the biosynthesis of agents with lipotropic activity. This relation is outlined briefly in the section below that deals with the mechanism of lipotropic action.

Choline

Choline is a quaternary ammonium base containing three methyl groups. Chloride, dihydrogen citrate, or other salts of choline are the forms in which it is available commercially. As an integral part of phospholipids, choline is a constituent of many plant and animal tissues. Since phospholipids are found in all living cells, it is thought that they are essential cellular components. The richest known dietary source of choline is egg yolk. Other good sources are liver, brain, kidney, heart, lean meat, yeast, soya bean meal, peanut meal, and wheat germ. Fruit, fruit juices, and vegetables are generally not good sources of choline. Neutral fats are essentially devoid of choline.[13] Free choline is detected in the afore-

mentioned food sources only in small amounts. Adequate data concerning the availability to man or animals of the choline present as complex phospholipids in food sources are not available; however, one study suggests that choline is absorbed better when given in the bound form as lecithin than when given as free choline.[14] Information concerning the average daily intake of choline by normal adult man is also meager. It is estimated that the normal adult consuming a usual diet ingests 250 to 600 mg. of choline daily.[15] A nutritious diet containing 100 gm. of protein and recommended for the treatment of patients with liver disease was calculated to contain 900 mg. of choline daily.[16] The choline requirement of normal man is not established. An absolute value for choline requirement probably cannot be established, since this may depend upon other conditioning factors in the diet, some of which are discussed later.

The level of free choline in the blood of normal persons ranges from 1 to 2 mcg. per milliliter, levels similar to those observed in other species (dog, cat, and rat).[17] The daily urinary excretion of choline by normal persons on average diets ranges from 2 to 4 mcg.[15a] After choline ingestion (2 to 8 gm.) only a small amount of free choline is recovered in the urine and no significant quantity in the stool.[18] The level of free choline in the blood of animals is not altered by the oral administration of choline but is elevated for short periods of time after its intravenous administration [19]; in studies of this, only about 10% of the administered choline was found in the urine. The rate of disappearance of choline from the blood is not greatly altered by hepatectomy or bilateral nephrectomy.[19] These animal studies suggest that choline given intravenously is rapidly metabolized or excreted by some other route. Approximately two-thirds of choline administered orally to normal adults was accounted for by the urinary excretion of trimethylamines,[20] choline derivatives with no significant lipotropic activity.[21] That the transformation of choline to trimethylamine results from an effect of the gastrointestinal flora on the former is indicated by several observations. No significant increase in urinary trimethylamine excretion follows the intravenous administration of choline.[18d] Bacteria degrade choline to trimethylamine in vitro. The oral administration of antibiotic agents (chlortetracycline, oxytetracycline, and penicillin) temporarily suppresses the urinary trimethylamine excretion after choline ingestion because these agents produce alterations in the bacterial flora of the intestinal tract.[22] It has been suggested that the alterations of significance occur in the upper small intestine. Administration of antibiotics thus appears to exert a choline-sparing effect. The physiological significance of the gastrointestinal flora in choline metabolism cannot be stated with certainty, but these studies indicate its importance.

Methionine

Methionine is a sulfur-containing amino acid with a labile methyl group. Rose has demonstrated that methionine is one of the eight essential amino acids needed for the maintenance of nitrogen balance in adult man.[23] The requirement of methionine for this purpose can be largely, but not entirely, replaced by dietary cystine.[24] An essential amino acid is one that is necessary for protein synthesis or other biological processes but that cannot be synthesized by the organism. A dietary source of methionine is thus necessary. The indispensability of methionine probably rests with its role alone or as a precursor of cystine (also a sulfur-containing amino acid) in tissue protein synthesis [25] and with its role as a source of labile methyl groups for the synthesis of choline and other compounds involved in methylation reactions.[26] Most plant and animal proteins contain significant quantities of methionine. For example, animal muscle contains about 3.3 gm. per 100 gm. and casein and lactalbumin 2.8 and 3.5 gm. per 100 gm. respectively.[27] Because of their high protein content, foods of animal origin generally provide more dietary methionine than do plant foods.

The daily requirement of methionine in the absence of cystine is estimated to be 1.1 gm. for normal adults, but a daily allowance of 2.2 gm. has been recommended.[23] The minimal methionine requirement for maintenance of nitrogen balance, however, may be modified by cystine contained in the diet, since it has been demonstrated that cystine spares methionine.[24] An adequate diet ordinarily insures an adequate methionine intake. For patients with liver disease or other disease states, the requirement of methionine is not known. The level of free methionine in the plasma of normal human subjects ranges from 0.2 to 1.5 mg. per 100 ml.[28] The daily excretion of free methionine in the urine of normal adults on average diets is about 2 to 8 mg. and of total methionine (free plus bound) 8 to 12 mg.[29] The urinary excretion of methionine is small in relation to total methionine intake in the normal adult and is changed relatively little by changes in the intake of protein.[29b] The significance of plasma levels and of urinary excretion values for methionine in terms of protein or amino acid nutrition is not established.

Mechanism of Lipotropic Action

Ingested choline is rapidly incorporated into liver phospholipids. This biochemical step may be essential to the function of phospholipids in fat transport [30] or fatty acid oxidation [31] or both. Deficiency of choline results in a deficiency of phospholipid synthesis and failure of fat transport or oxidation; as a consequence, fat accumulates in the liver. Methionine exerts lipotropic activity by providing methyl groups for the synthesis of choline.[10] When the availability of methionine (or methyl groups) is limited, the biosynthesis of choline is limited. Methionine can replace choline as a necessary dietary constituent since the latter is synthesized in vivo if methyl groups are available. Methyl groups from choline are less available, and therefore the converse does not hold. This relationship makes it apparent that the requirement of an organism for choline is dependent in part upon the methionine content of the diet, which in turn is ordinarily dependent upon its protein content. The lipotropic effect of protein foods is related to their content of methionine, choline, and other factors concerned with the availability or metabolism of methyl groups. It is recognized, however, that factors other than "methyl group deficiency" may be responsible for the production of some types of fatty liver lesions in experimental animals. For example, fatty liver lesions produced in rats

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by feeding them diets consisting principally of certain plant foods, synthetic diets deficient in lysine or threonine, or diets providing inadequate quantities of protein for short periods of time are not completely reversed by the feeding of choline, methionine, or vitamin B_{12}.[32]

The previous discussion indicates a relationship between methyl groups and choline synthesis. Labile methyl groups can be synthesized in vivo from several substances such as formate,[33] methanol,[34] and acetone.[35] Factors influencing methyl group synthesis affect lipotropic mechanisms by making these groups available for choline synthesis. Among the nutritional factors involved in the metabolism of single carbon units (methyl groups) are vitamin B_{12}, folic acid, and the citrovorum factor. The last is a derivative of folic acid, which is suited to the transfer of single carbon units, since it contains a formyl group not present in folic acid. Several studies suggest that vitamin B_{12} and folic acid function in transmethylation systems and that they are needed for the formation of methionine from homocystine, a synthetic amino acid not known to occur in food. The tissues of animals deficient in folic acid convert less C^{14}-labeled formate or methanol to methionine methyl or to choline than do animals given the same diets supplemented with folic acid or with citrovorum factor.[36] Some studies indicate a decreased synthesis of choline from C^{14} formate in rats fed a diet deficient in vitamin B_{12}.[37] Other experimenters failed to demonstrate this effect of vitamin B_{12} on choline synthesis.[38] That vitamin B_{12} and folic acid are involved in the transfer of methyl groups is also indicated by the observation that rats or chicks maintained on diets deficient in methyl groups, but containing homocystine, fail to grow unless vitamin B_{12} or folic acid is also provided.[39] The administration of methionine with such diets allows the animals to grow despite the absence of the vitamins.

These brief comments, which represent an oversimplification of the situation, illustrate the multiplicity of factors involved in lipotropic mechanisms. For more detail concerning the role of vitamin B_{12} and folic acid in the metabolism of single carbon fragments and their relation to methionine and choline synthesis, the reader is referred to reviews on these subjects.[40]

Most of the data concerning the mechanism of lipotropic action and the interrelation of nutritional factors involved with the synthesis and metabolism of single carbon units are derived from in vivo and in vitro animal studies and studies of bacterial metabolism. The applicability of these fundamental observations to human nutrition and to clinical situations cannot be stated until more extensive investigations of these are accomplished.

Nutritional Factors in the Pathogenesis of Liver Disease in Man

There is indubitable evidence derived from animal experiments that the functional and histological integrity of the liver depends upon certain specific nutritional factors.[41] Under experimental conditions, fatty liver and cirrhosis in animals result from dietary deficiency of protein, methionine, choline, betaine, vitamin B_{12}, and folic acid. Deficiency of cystine, methionine, vitamin E, and certain fractions derived from yeast results in liver necrosis and postnecrotic scarring.

The concept of cirrhosis of the liver in man resulting from disturbances in nutrition stems from the aforementioned fundamental observations. Evidence incriminating dietary factors in the etiology of human liver disease is of necessity less specific because it does not come about under carefully controlled experimental conditions. Fatty liver cirrhosis as it is produced in the experimental animal by dietary means finds a tempting correspondent in the fatty cirrhosis of the human liver. The latter is perhaps best typified in this country by the fatty cirrhosis in the alcoholic and in several other areas of the world by persons who suffer from the malnutrition syndrome, kwashiorkor. The fatty liver lesions in experimental animals and in man are not, however, histologically identical. In the former, the distribution of fat is largely centrilobular, and in the latter, periportal.

The best evidence that nutritional factors are involved in the pathogenesis of liver disease comes from a consideration of kwashiorkor, one of the major malnutrition syndromes existing in the world.[42] This disorder is seen in many tropical and subtropical areas. It occurs primarily in children in the weaning and postweaning periods. These children have hepatomegaly, retarded growth, alteration in skin and hair pigmentation, dermatoses, and edema. Anemia and gastrointestinal disturbances sometimes occur. Fatty infiltration and cellular necrosis or fibrosis are quite consistently found by liver biopsy or at autopsy. The diets of the populations of the areas in which this syndrome occurs are low in protein, especially that of animal origin. The disorder is almost certainly fatal without adequate treatment, which consists primarily of feeding protein such as skim milk powder with suitable carbohydrate.[43] With proper dietary treatment the fatty liver lesions can be reversed and the patient rehabilitated, but this is not always easy.

Surveys indicate that the incidence of liver cirrhosis is very high among African adults living in areas where kwashiorkor is prevalent.[44] Whether this cirrhosis is a sequel of fatty liver disease that occurred in childhood, whether it is the result of the continuing effects of dietary factors in adolescence and adulthood,[44] or whether it is the consequence of a metabolic process separate from that which causes the fatty changes is not finally established.[45] The relation of fatty changes to cirrhosis of the liver associated with alcoholism is also a matter of conjecture. The recent experimental work of Hartroft and associates supports the concept of a causal relationship between fatty liver changes and fibrosis.[46] Rats fed diets deficient in lipotropic substances developed fatty livers. By special staining techniques Hartroft demonstrated that the liver cells containing fat might coalesce and produce "fatty cysts." These cysts might eventually rupture and, presumably by bringing about an inflammatory reaction in extracellular areas, result in proliferation of connective tissue and distortion of liver architecture. The finding of residual cysts in fibrous trabeculae in patients with cirrhosis suggests that a similar sequence of events may take place in man,[47] but unanimity of opinion does not exist on this subject.[48]

Although most evidence indicates that kwashiorkor results from protein malnutrition and responds to the feeding of protein, the exact cause of this syndrome is not known. Choline, methionine, vitamin B_{12}, folic acid,

and other known B complex vitamins have been used as potential specific therapeutic agents but have not exerted convincing specific responses.[43] An increase in periportal fat, similar in distribution to that seen in patients with kwashiorkor, has been observed in the livers of rats fed corn meal, rice, or cassava. These lesions were prevented by feeding lysine and tryptophan but not by dietary supplementation with choline, methionine, or vitamin B_{12}.[49] These animal studies indicate that protein deficiency may result in periportal fatty liver lesions and suggest that an amino acid imbalance may be a factor of etiological importance in kwashiorkor. There is no conclusive clinical evidence, however, that this is the case. Dietary surveys have failed to indicate that lack of "labile methyl groups" or lack of essential amino acids is involved in the development of fatty liver and cirrhosis in some of the African population groups afflicted with kwashiorkor and a high incidence of cirrhosis.[50] Whether kwashiorkor results from a specific deficiency of known nutrients, from some discrepancy between protein and caloric intakes, from an amino acid imbalance, or from deficiency of some unidentified factor or factors contained in skim milk powder awaits further investigation.

Although patients with kwashiorkor and those with cirrhosis associated with alcoholism have some features in common, it has not been established whether or not the pathogenesis of these conditions rests on common ground. In addition to histological changes in the liver, in patients with kwashiorkor there have also been pathological findings of atrophy of enzyme-secreting cells of the pancreas, salivary and lacrimal glands, and small intestine.[51] These changes may in fact represent the primary lesions of kwashiorkor. Other groups of nonalcoholic, malnourished patients with liver disease have evidence of hemochromatosis.[52] These findings are not prominent features of liver disease associated with alcoholism and suggest that different factors may be operating in these situations. In addition, the incidence of primary liver carcinoma is much higher in the population in kwashiorkor areas than it is in patients with cirrhosis associated with alcoholism.[44]

Direct evidence relating dietary factors to the pathogenesis of fatty cirrhosis in the alcoholic is meager. It is generally agreed and accepted that the dietary intake of alcoholics is suboptimal and that the caloric intake derived from alcohol decreases the intake of calories derived from food. The food consumption patterns of patients with fatty cirrhosis suggest that diets composed largely of carbohydrate foods or providing inadequate protein are associated with the liver lesions.[47a] Persons who are steady daily drinkers for long periods of time but subsist on only moderately reduced intakes of food are prone to the development of fibrosis of the liver. Those who drink in sprees and who, while drinking, consume practically no food, are predisposed to the development of fatty changes in the liver that may completely reverse after abstinence from alcohol and the ingestion of even a meager diet.[53] More detailed knowledge concerning the dietary aberrations of alcoholics, a subject on which few data are available, would aid in further determining whether or not the ingestion of alcohol results in some disproportion in caloric intake in relation to intake of protein, B complex vitamins, fat, and carbohydrate. A diet in which a large proportion of the total calories consists of alcoholic beverages in all probability results in a disproportionate intake of nutrients. The animal studies of Best and his associates suggest that caloric imbalance may be a factor involved in the pathogenesis of liver disease.[54] Fatty infiltration and fibrosis of the liver, lesions that did not develop in pair-fed control animals, occurred in rats fed alcohol or isocaloric amounts of sucrose. These lesions were prevented by dietary supplements of choline, methionine, or casein. It was concluded that the increased caloric intake resulted in a relative choline deficiency regardless of whether the additional calories were derived from alcohol or from sucrose. This conclusion is not supported by other studies by Klatskin and associates concerning the effect of prolonged alcohol ingestion on the livers of rats.[55] Significant histological evidence of fatty infiltration or fibrosis of the liver was not noted in rats given diets containing protein, choline, and vitamins sufficient to prevent fatty liver changes in control animals fed ad libitum. Chemical analysis revealed, however, that rats given alcohol had more fat in the liver than those of other control groups, including isocalorically fed animals receiving no alcohol. Klatskin and his associates suggest that alcohol, rather than a nonspecific increase in caloric intake, may increase the choline requirement. Clinical investigations analogous to these reported animal experiments have obviously not been done, but it has been suggested that in kwashiorkor a discrepancy may be involved between protein intake and caloric intake or intake of other nutrients.

Evidences of undernutrition are frequent in patients with cirrhosis associated with alcoholism, whereas evidences of malnutrition or specific deficiency diseases occur with less frequency. Undernutrition or starvation, however, rarely results in significant liver disease.[56] The incidence of liver disease is greater among groups of people subjected to malnutrition caused by qualitatively more deficient diets.[57] Overindulgence in alcoholic beverages does not inevitably result in undernutrition nor in hepatic lesions. Evidence of liver disease may occur in alcoholics who appear well nourished or indeed obese and may not be apparent in undernourished alcoholics.

Although recent emphasis has been on the nutritional aspects of cirrhosis of the liver, and these are undoubtedly important, it has not been definitively settled whether or not alcohol exerts a direct toxic action on the liver. Cirrhosis is not consistently produced in animals by feeding them alcohol in an adequate diet.[58] It is possible, of course, that the combination of nutritional deficiency and alcohol ingestion is prerequisite for the development of liver disease. The analogy to the increased susceptibility of animals maintained on deficient diets to hepatotoxins such as carbon tetrachloride is obvious.[59] Volwiler and associates observed that the administration of a nutritious diet resulted in functional and histological improvement of the liver in one patient, in spite of the continued administration of alcohol.[60] Patek and Post reported that alcohol given for six to eight months to four patients who had been treated for liver disease had no apparent adverse effect.[61] These observations provide clinical evidence against a direct hepatotoxic action of alcohol.

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Metabolism of Lipotropic Factors in Patients with Liver Disease

Several recent reports dealing with the metabolism of choline and methionine in patients with liver disease are pertinent because they bear on a better understanding of the potential therapeutic usefulness of these factors and offer an indirect approach to determine whether or not deficiency of these factors exists in patients with liver disease.

Cornatzer and associates have investigated the rate of turnover of phospholipid after the administration of radioactive phosphorus in normal persons and in patients with liver disease.[62] The rate of phospholipid turnover was not altered in normal persons after the administration of choline or methionine. Although the normal rates of synthesis varied considerably, the rates in the same person over periods of several months were relatively constant. The initial rates of phospholipid synthesis in patients with cirrhosis of the liver were within the normal range. After a single large dose of choline or methionine, however, significant increases in phospholipid synthesis occurred in some patients. After patients were treated with lipotropic agents and an adequate diet for several months, this stimulatory effect of added choline or methionine was not apparent. The stimulatory effect of lipotropic agents did not occur in patients with viral hepatitis, a situation not usually associated with fatty changes in the liver.[63] Other similar studies suggest that the most significant increases in phospholipid synthesis occurred in patients with fatty infiltration of the liver, in contrast to patients with fibrosis or necrosis, in whom no significant change occurred in phospholipid synthesis rate or in liver histology after choline or methionine was administered.[64] The correlation between increased rate of phospholipid synthesis and decrease in liver fat, however, was not consistent since the former but not the latter was found in some patients.[65] These studies have been interpreted to indicate that patients with fatty cirrhosis are deficient in choline or related compounds although some inconsistencies in this concept are apparent. For reasons that are unexplained, an increased phospholipid turnover was noted after choline was administered to a patient with adhesive pericarditis.[66] The studies do not provide evidence that the addition of choline to a nutritious diet enhances phospholipid synthesis any more than might occur from dietary therapy alone over a period of several months. Although these studies do not provide conclusive evidence for deficiency of lipotropic factors in fatty liver disease in man, this method of study warrants further consideration.

The metabolic fate of choline administered to normal persons and to patients with liver disease is the subject of a series of investigations by de la Huerga and associates.[67] Observations concerning the metabolism of choline in normal persons were discussed in a preceding section. A delay in the excretion of trimethylamine occurred in patients with liver disease; they excreted less of this metabolite in the urine after oral administration of choline than did normal persons. Choline or trimethylamine was not found in the feces. These investigators suggest that the absorption of choline from the intestinal tract is enhanced in patients with liver disease and imply that there is a deficiency of choline in these patients.

Whether the decreased excretion of trimethylamine by patients with liver disease after oral administration of choline is caused by increased absorption and utilization of choline, by differences in the intestinal flora of these patients as compared to that of normal persons, or by differences in the way choline or its derivatives are metabolized in the presence of liver disease is not finally established. The evidence indicating that most of the orally administered choline is transformed to trimethylamine in the gastrointestinal tract suggests that only a limited amount of ingested free choline may be absorbed in a form capable of manifesting lipotropic activity, a quality that trimethylamine lacks.

Several studies concern the metabolism of methionine (and other amino acids) in patients with liver disease. Plasma levels of methionine are normal or elevated in these patients.[68] Their average urinary excretion value for methionine is high, although the values of some patients fall within the normal range.[69] Improvement in the liver disease may be accompanied by progressive decreases in excretion of urinary methionine.[70] The rate of removal from the blood of intravenously administered methionine is impaired in some persons with chronic cirrhosis.[288] These studies contribute to knowledge concerning the metabolism of methionine in patients with liver disease; however, their specific applicability to fatty liver disease is questioned since the studies were not limited to patients with this clinical condition. The increases in plasma and urinary methionine noted in patients with acute and chronic liver disease indicate that methionine is available. They are difficult to interpret as being indicative of methionine deficiency, unless this deficiency results from some as yet unexplained metabolic defect related to the utilization of this amino acid.

The demonstration of a favorable metabolic response after administration of choline and methionine to patients with liver disease would provide a rationale for their use in treatment and offer indirect evidence that a deficiency of these factors existed. A sparing of urinary nitrogen with resulting increased positive nitrogen balance has been attributed to lipotropic agents administered to patients with chronic liver damage who were maintained on adequate protein intakes.[71] Other studies failed to confirm this observation, since urinary nitrogen excretion was not decreased after the oral administration of choline and methionine to patients with liver disease. Increases in nitrogen balance occurring during the administration of these agents could be accounted for by the nitrogen they contained,[72] and it was further demonstrated that positive nitrogen balance was most economically and effectively achieved in patients with liver disease by providing adequate dietary protein rather than by supplementing diets with choline and methionine or by giving testosterone propionate intramuscularly.

Lipotropic Agents in the Treatment of Liver Disease

The therapeutic efficacy of a nutritious diet and supplements rich in vitamin B complex provides evidence that hepatic cirrhosis results from nutritional deficiency.[73] Recent investigations have been directed to-

ward elucidating the factor or factors contained in a nutritious diet or accompanying its administration that might account for its therapeutic value. Clinicians drew upon the convincing evidence derived from animal experiments in an attempt to elucidate the factors involved. It seemed reasonable that lipotropic factors such as choline and methionine, which are effective in protecting against fatty liver and cirrhosis in experimental animals, might provide specific therapy for the treatment of grossly similar pathological conditions in man. Reports appeared attesting to the efficacy of these agents as dietary supplements in the treatment of liver disease.[74] The methods of study employed usually lacked adequate statistical and dietary control and failed to provide convincing evidence that dietary supplements of lipotropic factors and vitamins replaced an adequate diet as optimal nutritional therapy for these patients.

Studies comparing one dietary regimen with another are limited by the naturally occurring variation in the severity of the liver disease, the unpredictability of its course, and the difficulty of establishing criteria of improvement. For example, alcoholics with acute fatty liver disease, the situation in which lipotropic factors might be expected to be of most value, often rapidly improve clinically after hospitalization, withdrawal of alcohol, and provision of food.[75] The former two factors, which are very difficult to evaluate experimentally, have not always been given enough consideration. Studies utilizing only tests of liver functions and the clinical response of the patient in evaluating therapeutic measures are of limited value, since favorable changes in these are not necessarily accompanied by improvement in liver histology.[75c] Furthermore, the failure of a lipotropic or other nutrient supplement to enhance the therapeutic value of the diet does not mean that the supplement may not be implicated in the pathogenesis or treatment of liver disease; it is possible that the nutrient in question may be contained in the diet in quantity sufficient to be therapeutically effective. One obvious method whereby possibly significant factors in diets can be eliminated as agents of value is to provide patients with diets that are essentially devoid of lipotropic factors. After initial control periods of observation, specific lipotropic agents could then be added to such a regimen and their effect observed upon liver histology, tests of liver functions, and clinical status of the patients. If the courses of patients with fatty cirrhosis of the liver who show no evidence of improvement on diets deficient in lipotropic factors were favorably influenced by the addition of choline and/or methionine or other nutrients, the result would strongly indicate that lipotropic factors are specific therapeutic agents. It would also imply that lack of these factors is involved in the pathogenesis of liver disease. Several investigators have recently utilized this experimental approach for the study of patients with fatty liver disease.

Eckhardt and associates [75a] studied four patients with active liver disease who were provided with diets essentially devoid of protein and were given amino acids intravenously as the major source of protein and lipotropic substances. (The basal diet contained 30 to 100 mg. of choline.) The patients received a multiple vitamin capsule every day; their daily intakes ranged from 1,700 to 4,500 calories. Intravenous injections of methionine, amounting to 2 to 4 gm. daily, were given as a constituent of the amino acid mixture. During a two to four-week period of observation on this regimen, all patients improved clinically, and liver function returned toward normal. Size of the liver decreased in two patients. Distinct improvement in liver histology was found in one patient in whom serial liver biopsies were done. Interestingly, clinical improvement and improvement in liver function tests occurred in one of the patients who had a negative nitrogen balance during a two-week period. Liver biopsies were not done in the study of this patient.

The effect of protein starvation and of protein feeding on the clinical course, liver function, and histochemistry of three patients with fatty cirrhosis is discussed in another report.[75c] For 8 to 13 days these patients were given calorically adequate diets that were essentially devoid of protein. In addition, each patient was given a multiple vitamin capsule daily. During the period of protein starvation and concomitant negative nitrogen balance, clinical improvement was seen in each patient, including decrease in liver size and tenderness, and tests of liver function returned toward normal. In fact, the clinical findings and laboratory tests improved enough during the period of protein starvation that further improvement by these criteria that might have followed the addition of protein or other lipotropic substances would have been difficult to detect. Serial liver biopsies failed to reflect the improvement noted by other criteria, except for a moderate reduction in liver fat content after choline was administered to one of the patients (12 gm. orally every day for six days). Significant return of liver morphology toward normal did not occur until after adequate dietary protein was provided. This study illustrates the fact that during relatively short periods of time patients with fatty liver disease may show evidence of improvement even if fed diets grossly deficient in protein. The morphological improvement noted after feeding of protein further attests to the therapeutic value of an adequate diet. This study illustrates emphatically the necessity of including adequate control studies in attempting to evaluate the efficacy of specific therapeutic agents; however, it does not indicate what alcohol withdrawal and rest in the hospital might have contributed to the improvement noted during the initial periods.

That alcohol withdrawal and rest were not primarily responsible for the improvement noted is suggested by the studies of Phillips and associates.[76] They reported the comparative effects of a "purified" diet and an adequate diet on the courses of three alcoholic patients with fatty liver cirrhosis. The purified diet, which was employed for the initial 8 to 10 days, consisted of solutions of glucose (1,600 calories), minerals, and vitamin supplements. Two of the patients were given additional thiamine as treatment for coexisting Wernicke's disease. In contrast to the results of the study previously discussed, these three patients did not improve clinically, nor was there improvement in hepatic function tests or in liver fat content during the administration of the purified diet. After 8 to 10 days of an adequate diet, improvement in liver function and decreases in hepatic fat occurred in two patients and in the third patient after

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14 days. The adequate diet consisted of a regular hospital ration containing 2,000 to 2,500 calories, 80 to 100 gm. of protein, 200 to 250 gm. of carbohydrate, and about 110 gm. of fat daily. The therapeutic value of an adequate diet is again apparent. The failure of these patients to improve during the administration of a purified diet tends to relegate alcohol withdrawal and bed rest to roles of minor significance.

When patients with fatty cirrhosis failed to improve on the purified diet, opportunity was taken to evaluate the efficacy of choline by Phillips and Davidson.[77] Five patients with fatty cirrhosis were studied in a similar manner and were provided with the purified diet as outlined previously; in addition, they were given choline orally for 4 to 10 days. The result was neither decisive nor consistent. In two patients the effect may have been beneficial, but three were not benefited by administration of choline. An isocaloric (1,600 calories), well-balanced diet containing only 50 gm. of protein resulted in improvement in the liver disease and liver histology of these three patients. The reason for the great difference in response of these apparently similar patients is not known. These observations indicate that the therapeutic factor or factors responsible for improvement in the liver disease are dietary components, probably not calories as such. They fail, however, under the conditions of study employed, to establish choline definitely as a consistent, specific therapeutic agent. The authors suggest that the pathogenesis and treatment of liver disease of the alcoholic may be related to multiple factors.

A recent report by Best and his associates [32a] concerning the effects of dietary protein deficiency on total lipids and distribution of stainable fat in the livers of rats may be pertinent to the discrepancies noted in the clinical studies reviewed. Accumulations of fat in a centrilobular distribution occurred in animals maintained on choline-deficient diets. Animals fed protein-deficient diets had less massive accumulations of fat, but accumulations were seen in periportal areas and were not completely prevented by supplementary choline. These differences in fatty liver lesions were greatest when the deficiency was of mild degree and of short duration. More prolonged and severe deficiencies resulted in a generalized distribution of fat in the liver.

These studies also suggest that multiple factors may be involved in the pathogenesis of fatty liver lesions in animals and that the quantity and distribution of fat in the livers of animals given deficient diets depend not only upon the nature of the deficiency but upon its degree and duration. Best and co-workers support the hypothesis that protein deficiency or amino acid imbalance is responsible for the periportal type of fatty liver lesions. They conclude that the lipotropic activity of protein depends upon its methionine content and the qualitative and quantitative nature of the amino acids it contains. The clinical significance of these observations is not clear, but these factors deserve careful consideration and evaluation in future clinical investigations.

Although the aforementioned clinical studies contribute valuable information concerning the natural history of fatty cirrhosis and outline more quantitatively the gross dietary requirements necessary to bring about improvement and the minimal conditions at which improvement does not occur, they do not provide conclusive evidence for a specific therapeutic effect of choline. Further clinical investigations utilizing a similar experimental approach will be awaited with interest.

Summary and Conclusions

That dietary deficiency of lipotropic factors such as choline and methionine results in fatty cirrhosis of the liver in some animal species can be stated with certainty. Available in vivo and in vitro animal experiments provide information that allows for the formulation of reasonable hypotheses concerning the mechanisms of lipotropic action and the interrelation of nutritional factors involved in these mechanisms. Although it is probable that similar biochemical mechanisms function in man, the determination of whether this is so or not awaits further clinical investigations.

There is a paucity of information concerning choline and methionine in the nutrition of normal man. Recent studies on the metabolism of choline and methionine in normal man indicate interest in this field and have contributed significantly to knowledge of this subject. To date, however, metabolic studies have failed to indicate convincingly that a deficiency of choline or methionine exists in patients with liver disease.

Deficiency of dietary factors or alterations in the pattern of diet are implicated in the production of fatty cirrhosis of the liver in man, although the evidence for this is circumstantial and inductive. The best evidence that fatty cirrhosis occurs in man in close relation to nutritional deficiency comes from observations on children with the protein malnutrition syndrome, kwashiorkor. The specific factor or factors involved in the production of this malady are not known. Convincing therapeutic responses to specific agents of potential value such as choline, methionine, folic acid, and vitamin B_{12} have not been reported. Present therapy for patients with this syndrome consists of an adequate intake of dietary protein of good biological value with suitable carbohydrate. The relation between the fatty liver lesions associated with kwashiorkor or with alcoholism to subsequent hepatic fibrosis and chronic cirrhosis is not clear.

Dietary factors are also implicated in the development of fatty cirrhosis of the liver associated with alcoholism. The most critical studies reported to date were designed to test the therapeutic value of choline used in patients with fatty cirrhosis of the liver associated with alcoholism. These studies do not provide, however, conclusive evidence that choline exerts a specific therapeutic effect in this type of fatty liver disease in man. Contrariwise, controlled clinical studies consistently and convincingly demonstrate the therapeutic value of well-balanced diets containing adequate quantities of protein. There is no valid evidence that supplementing an adequate diet with choline, methionine, other lipotropic agents, or vitamins brings about more prompt or more complete recovery than might be accounted for by the diet alone. The conclusion is justified that patients with fatty cirrhosis of the liver receive optimal nutritional therapy if they are provided with adequate, well-balanced diets. The factor or factors that might account for the therapeutic efficacy of the diets employed in the treatment of patients with fatty cirrhosis of the liver remain elusive.

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IRON DEFICIENCY ANEMIA IN INFANTS

GUEST EDITORIAL

Robert L. Jackson, M.D.

Hypochromic anemia is the most common nutritional deficiency in children in the United States and occurs most frequently during the latter half of the first year after birth. Prevention rather than treatment of hypochromic anemia is our goal. The iron available at birth depends on the adequacy of the mother's diet, the length of gestation, and the placental blood allowed to reach the infant. Iron is stored in the liver of the fetus during the last six weeks of normal gestation. The amount stored is influenced considerably by the nutritional status of the mother. Infants born prematurely are denied this crucial period of iron storage and have a greater need for growth. About 100 ml. of blood will enter the term infant's body if the umbilical cord is not clamped until pulsations cease. This amount of blood will make available approximately 45 mg. more iron for storage. This amount of iron may seem insignificant, but it approximates the iron in the diet of many an infant during the first six months of extrauterine life.

Four to six months after birth, the hemoglobin value reflects the dietary regimen and the incidence of infection. Hypochromic anemia occurs most commonly in infants receiving excessive amounts of milk and insufficient amounts of solid foods. An infant receiving only the slight amount of iron found in milk generally has a slow decrease in hemoglobin level during the latter half of the first year. If his original iron store is poor, an iron-deficiency anemia will appear in late infancy. It is wise to begin the addition of iron-containing foods at the time when the infant reaches his minimum hemoglobin level (10.5 to 11.5 gm. per 100 ml.), and that time is about three months after birth. The requirement of iron is about 5 mg. daily. The common iron-containing foods fed to young infants, egg yolk and green vegetables, provide 1 to 2 mg. daily at most. The sieved meats provide 0.5 to 1.7 mg. to the ounce. Many of the special infant cereals have iron added in amounts providing 2.5 to 4 mg. to the serving of ⅓ oz. (10 gm.). The infant born at term of a healthy well-fed mother will maintain a good hemoglobin level for at least six months if it is free from infection. If he receives some iron-containing foods daily after the fourth month, probably no other iron supplements are necessary. However, in view of the many variables involved in determining the iron available to the infant and the difficulty in evaluating each variable, it seems wise to advocate the addition of 5 mg. of iron daily to the diets of full-term and prematurely born infants from 3 to 6 months of age. In a recent study we [1] found that ferrous iron permitted significantly higher hemoglobin values in well infants than did ferric iron. It is often stated that iron is not absorbed when given in milk or with meals high in phytates or phosphates. The small amount of ferrous iron (5 mg.) used in our study was added to the milk, and satisfactory hemoglobin responses were observed. Schulman, Smith, and Stern [2] found that iron given to prematurely born infants before the third or fourth month after birth produces little clinical response. Iron after the third or fourth month not only is essential but is well utilized and will prevent the development of hypochromic anemia.

Professor and Chairman, Department of Pediatrics, University of Missouri School of Medicine, Columbia, Mo.

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NATIONAL HOSPITAL WEEK

Every year the President sets aside a special week in which hospitals can endeavor to improve the public's awareness of the services the hospitals are prepared to give and in which the hospitals can take stock of how well they are meeting community needs. This is not a fund-raising week but a week in which to foster better understanding. This year it will be observed from May 6 to 12, and the theme will be "Your Hospital—For You and Your Community." Special emphasis this year is being placed on disaster planning. In recognition of the fact that preparations to meet such disasters as floods, fires, hurricanes, and tornadoes are quite as important as preparations for an enemy air attack, the American Hospital Association has changed the name of its Civil Defense Committee to the Committee on Disaster Planning. A civil disaster of any of the types mentioned may need to use the resources of the small community hospital as well as those of the large metropolitan hospital in any part of the country. In order to facilitate disaster planning and to help hospitals formulate their plans in ways that have proved effective, the American Hospital Association has issued a brochure entitled "Principles of Disaster Planning for Hospitals" in which are described the necessary steps to be taken. Plans should be flexible and reviewed often enough to keep them abreast of changing situations. Also it is especially important to orient and train new employees in their emergency duties. The two types of emergency action required are evacuation, if the disaster involves the hospital itself, and expansion of its facilities, if the disaster occurs outside the hospital. The American Hospital Association brochure, if carefully studied, will reveal the problems of disaster and the value of implementing a workable plan if disaster strikes.

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CLEFT LIP AND PALATE

Some degree of cleft lip and palate occurs in about one in every 850 live births. There is a wide difference, however, in reports of incidence, and the apparent increasing incidence may merely reflect more accurate statistics, the effect of laws requiring the reporting of all congenital anomalies, or a greater number of conceptions resulting in live births.[1] Canick [2] classifies cleft lips as (1) simple, in which there is a unilateral cleft without an associated cleft of the maxilla; (2) complete cleft of lip and maxilla; and (3) incomplete cleft, with bridging between both edges of the cleft; and cleft palates as those involving (1) the soft palate only, (2) the hard and soft palate and extending no further than the incisive foramen, (3) the hard and soft palate and alveolar arch of the maxilla on one side—usually associated with unilateral cleft lip, and (4) the hard and soft palate and alveolar arch of the maxilla on both sides—usually associated with bilateral cleft lip. Lutz and Moor [3] found that in about 65% of cases the cleft is bilateral. Almost every conceivable causative factor has been suspected of producing this deformity—but in most cases with scant evidence. In animal experiments it has been found that a deficiency of riboflavin or pantothenic acid in the diet of the mother during pregnancy, the administration of an excess of cortisone or hydrocortisone (compound F), or a deficiency or excess of vitamin A will cause an appreciable increase in the number of offspring born with cleft palate (and other deformities). Although rubella during pregnancy increases the incidence of congenital deformities in human beings, this does not seem to apply to cleft lip and palate. A genetic factor is suggested by the fact that more than one member of a family has this deformity in about 20% of cases.[1]

The results of surgical treatment have not always been successful, and, according to Pruzansky,[4] failures are due to poorly conceived, badly executed, or ill-timed operations. Trusler and his co-workers [5] stated that postoperative maldevelopment may result from failure in healing or excessive surgical trauma, scarring, tension, or loss of tissue. The most common surgical error resulting in maldevelopment is wiring or other forcible correction performed too early in infancy. Another factor is undue tension in lip repair. The greater the number of operations on a given patient, the greater the interference with the normal growth and development of the involved parts. Although there appears to be general agreement that choosing the optimum time for operation is important to both the cosmetic and the functional result, there is still a difference of opinion as to the age at which surgical repair should be undertaken. In most hospitals lip repair is performed when the child is between 4 and 6 weeks old, but in the New York Hospital it is done immediately after birth.[6] This is an aid to feeding and obviates the necessity for the mother and child to return to the hospital. On the other hand, Le Mesurier [7] believes the best results are obtained if the lip is repaired when the infant weighs 12 lb. (5,443 gm.), regardless of age. Battle [8] advocates repair of the palate when the child is about one year old, so that normal speech may develop without special training. This does not hold if the child is deaf or mentally subnormal, if the parents speak indistinctly, or if the home environment is poor. The disadvantage of early operation is that any operation for this condition in early life will result in some limitation of normal growth and development, but Trusler did not observe maldevelopment of the maxilla as a result of closures of the hard palate in children between 18 and 24 months of age. Peer and his co-workers [9] believe that it is important to accomplish maximal repair before the child reaches school age, as in this way he will be less apt to be treated as a curiosity by his school mates. According to Pierce and his co-workers,[10] orthodontic treatment if required should be started as soon as active cooperation can be obtained—usually at about age 4.

Because many factors are involved, no simple formula can be offered and the type of operation and time for its performance must be determined for each individual patient. The plastic surgeon working alone cannot be expected to know when a child requires special speech therapy, when he should have dental braces, and many other matters not within his purview. If he merely refers the patient after operation to another specialist, the second specialist will not know the conditions existing before operation and may inadvertently work at cross purposes with the surgeon. Therefore, it has been found that the best results can be obtained if a team, consisting of a pediatrician, plastic surgeon, otorhinologist, pedodontist, orthodontist, dental prosthetist, psychologist, speech therapist, social worker, and nurse, collaborates. Such teams do not need to convene at one place and one time but must be taught to think in terms of the potentialities of the other members and be able to talk in the special language of those members. The operation of such a team assures that the right thing is done by the right person at the right time regardless of which member is consulted at any stage of the treatment.[11] In the field of speech therapy alone, preventive work started early not only will obviate need for special treatment later but also will give better end-results. Although perfect results from both the cosmetic and the functional standpoint can never be achieved, better operations performed earlier than in the past and with more competent teamwork are producing impressive results.

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8. Battle, R. J. V.: The Past, Present, and Future in the Surgery of the Cleft Palate, Brit. J. Plast. Surg. **7**: 217 (Oct.) 1954.

9. Peer, L. A.; Hagerty, R.; Hoffmeister, F. S., and Collito, M. B.: Repair of Cleft Palate by the Bone Flap Method: Group Evaluation of Cases, J. Internat. Coll. Surgeons **22**: 463 (Oct.) 1954.

10. Pierce, G. W.; Terwilliger, K. F.; Pennisi, V., Jr., and Klabunde, E. H.: Early Orthodontic Treatment in Cleft Palate Children, Plast. & Reconstruct. Surg. **16**: 3 (July) 1955.

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ORGANIZATION SECTION

QUARTERLY CUMULATIVE INDEX MEDICUS

Volume 54 of the Quarterly Cumulative Index Medicus, covering literature for the last half of 1953, has been mailed to subscribers and is now available for purchase from the Order Department of the American Medical Association, 535 N. Dearborn St., Chicago 10. Copy for volume 55 (January-June 1954), which is being reproduced at present, should be in print by the end of summer.

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

With a total registration of 975 medical educators, practicing physicians, and representatives of state licensing boards, specialty boards, and medical societies, the 52nd Annual Congress on Medical Education and Licensure set a new attendance record that exceeded last year's figure by almost 300. The meeting, held Feb. 11-14 in Chicago, was sponsored by the Council on Medical Education and Hospitals of the American Medical Association, the Federation of State Medical Boards of the United States, and the Advisory Board for Medical Specialties.

Fifty speakers, panel members, and moderators focused attention on five major subjects: a guide to the essentials of a modern medical practice act, a new program for evaluating the graduates of foreign medical schools, problems related to clinical faculty appointments and the private practice of medicine, current problems in residency training programs, and new approaches and experiments in the field of undergraduate medical education.

Liveliest discussion during the congress centered on the final report of a federation committee, which for the past three years has been studying the essentials of a modern medical practice act. The federation approved the report in principle after deleting two provisions and amending the title to read "A Guide to the Essentials of a Modern Medical Practice Act." The guide contains 11 sections covering the purpose of a medical practice act; a definition of the practice of medicine; recommendations on the establishment and composition of a licensing agency or board; recommendations on licensure requirements, examinations, licenses without examination, and grounds for suspension and revocation of licenses; definition of unlawful practice of medicine and violations and penalties; proceedings for revocation and suspension; injunction clause; and rules and regulations to be adopted by licensing agencies.

The introduction of the committee report pointed out:

> The recognition of a need for a Guide to the Essentials of a Modern Medical Practice Act by the Federation is confirmed by the work of the committee. This need stems from the study of many medical practice acts which show wide variation in their requirements and regulations. It is hoped this compendium may serve at least two purposes:
>
> 1. To serve as a guide to those states and territories which may adopt a new medical practice act or may be amending existing laws.
>
> 2. To encourage standardization of requirements and of regulations to better facilitate reciprocity and endorsement.
>
> The Essentials of a Modern Medical Practice Act are intended to serve only as advisory to licensing agencies.

Two controversial provisions were deleted from the guide. One of them, dealing with the composition of a licensing agency or board, would have recommended that members be selected "only on recommendation of official professional societies." The other deleted provision, which would have been included under grounds for suspension and revocation of licenses, read as follows: "Practicing medicine as the partner, agent, or employee of a person who does not hold a license to practice medicine, or practicing medicine as an employee of an association or corporation; provided however, a licentiate holding a license to practice medicine may accept employment from a person, partnership, association or corporation to examine and treat the employees of such person, partnership, association or corporation."

The federation by a close vote defeated an amendment that would have deleted the following provision as one of the minimum requirements for admission to an examination for licensure: "That an applicant satisfactorily completed a one-year internship approved by the licensing agency." That provision was kept in the guide as one of the suggested minimum requirements. By unanimous vote the federation also approved in principle a tentative draft of a proposed program for evaluation of graduates of foreign medical schools seeking hospital positions in the United States. The program was presented in a revised report of the Cooperating Committee on Graduates of Foreign Medical Schools, representing the federation, the A. M. A. Council on Medical Education and Hospitals, the Association of American Medical Colleges, and the American Hospital Association. The committee emphasized that the following two principles should guide the development of any program for evaluating graduates of foreign medical schools:

> 1. The primary concern must be for the health care of the American public. The responsibility to share our educational opportunities in medicine with other countries lacking similar opportunities is recognized, but it should not be allowed to have any deleterious effect on our primary concern. Thus, before assuming responsibility for the care of patients as interns or residents, all graduates of foreign medical schools (immigrants, exchange students and American graduates of foreign medical schools) should give evidence, as nearly as can be measured, of having reached a level of educational attainment comparable to that of students in our own schools at the time of graduation.
>
> 2. The primary objective of this Committee is to devise an effective mechanism for measuring educational attainment in the absence of intimate and continued knowledge of the educational background of foreign physicians. This mechanism should provide hospitals with pertinent information regarding the medical qualifications of foreign trained physicians seeking positions as interns or residents. It should not interfere with the

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hospital's privilege of making its own selection among qualified physicians, nor should it serve as a substitute for or interfere with the normal licensure procedures of the various state boards.

The proposed plan calls for establishment of a central administrative unit to conduct the program, study the results, and collect information on medical education abroad. The central staff would evaluate the medical credentials of foreign trained physicians desiring to serve as interns or residents in American hospitals. Basic requirements for applicants would include satisfactory evidence of at least 18 years of total formal education, including a minimum of 32 months in medicine exclusive of any time that in the United States would be considered as premedical study or internship. Applicants with satisfactory credentials then would take a screening examination in the basic medical sciences and the major clinical sciences, to determine their medical knowledge and their degree of facility in reading and writing English. Successful applicants then would be certified to whatever hospitals or other organizations they themselves might select.

The largest audience of the congress was drawn by a Monday morning symposium on "Problems Related to Clinical Faculty Appointments and the Private Practice of Medicine." Dr. George S. Klump of Williamsport, Pa., member of the A. M. A. House of Delegates, presided over the session, which was sponsored by the A. M. A. Council on Medical Education and Hospitals with the cooperation of the A. M. A. Council on Medical Service. The latter council is engaged in a study of the various problems involved in the practice of medicine by full-time faculty members in medical schools.

Dr. Robert L. Novy of Detroit, member of the Council on Medical Service, reported on a summary of responses to a medical school questionnaire. He said that 97% of the answering schools feel that it is either necessary or partially necessary to supplement faculty salaries with private practice arrangements. He also reported that the schools are much more satisfied with the present situation than are the county medical societies. Dr. Willard A. Wright of Williston, N. D., Chairman of the Committee on Medical and Related Facilities of the Council on Medical Service, gave a summary of responses to a medical society questionnaire. State societies, he reported, seem to be less critical than county societies of certain aspects of private practice by faculty members. Where difficulties have occurred, he pointed out, they usually have resulted from a breakdown in liaison between schools and profession. He said members of the profession are more concerned over the possible effects of certain practices on the future of medical education and the private practice of medicine than they are over loss of patients and income.

Mr. Edwin J. Holman, staff associate in the A. M. A. Law Department, reported on legal angles of the problem. As a general rule, he said, an unlicensed person, corporation, or entity cannot practice medicine. He pointed out, however, that a minority view finds exceptions to the general rule and that varying legal philosophies can influence legislators and judges in matters involving public policy. Dr. Joseph C. Hinsey, Ph.D., director of New York Hospital-Cornell Medical Center, made a strong plea for understanding and cooperation between medical schools and practicing physicians. "The medical school administrations must see to it that they do not compete unfairly with the practicing profession," he said, "and by the same token the profession should recognize the needs of our medical schools. Let's not confuse our code of medical ethics with medical economics."

Dr. David H. Poer of Atlanta, Ga., member of the Committee on Medical and Related Facilities of the Council on Medical Service, was unable to attend the congress, but his notes were read by Dr. Klump. Dr. Poer reported that most physicians, after examining the problem, conclude that they must do whatever is best for the future of medical education. They believe, he said, that the medical schools and the profession must work together for a solution. The Mississippi State Medical Association presented a statement urging immediate solution of the problem by the A. M. A. House of Delegates and declaring that no policy is in effect a condoning of the present situation.

The entire opening day of the congress was devoted to a conference on graduate medical education, cosponsored by the Council on Medical Education and Hospitals and the Advisory Board for Medical Specialties. Dr. Edward H. Leveroos, Director of the Council's Division of Hospitals and Graduate Education, led off the program by declaring that "we have reached the stage in the development of the residency system in this country where we must examine with meticulous care this phase of medical education which has grown so rapidly." Discussing residency training in hospitals not affiliated with medical schools, Dr. Alexander M. Burgess, director of medical education at Newport Hospital, Newport, R. I., and Miriam Hospital, Providence, R. I., recommended supervision by a single individual as full-time or part-time director of education.

In a paper on residency training in university hospitals, Dr. Carl A. Moyer, Bixby Professor and head of the department of surgery at Washington University School of Medicine, said that "the individual graduate student must be permitted to exercise gradually increasing responsibility in the care of patients, the teaching of medical students, the administration of the department and the solution of internal hospital problems." Dr. Julius H. Comroe Jr., professor and chairman of the department of physiology and pharmacology at the University of Pennsylvania Graduate School of Medicine, proposed the establishment of regional graduate schools of medicine to give basic medical science courses that would be integrated with hospital residency training programs.

Dr. Howard P. Lewis, professor and head of the department of medicine at the University of Oregon Medical School, described a personal, "family-style" method of teaching basic science and said "there is no better place than the patient's bedside to study and apply the basic knowledge, concepts and skills of medicine." Speaking on degree programs and investigation, Dr. Raymond D. Pruitt, professor of medicine and associate director at the Mayo Foundation for Medical Education and Research, commented that "the clinician who aspires to contribute materially to knowledge of disease

almost certainly will find it increasingly desirable to avail himself of concepts or methods derived from the fundamental sciences of physiology or biochemistry." Dr. Lawrence C. Kolb, professor of psychiatry at Columbia University College of Physicians and Surgeons, suggested that six weeks to six months of concentrated training in psychiatry may give the student physician better understanding of both himself and his patients.

In the session on new approaches to undergraduate medical education, Dr. Russell Meyers, professor of surgery and chairman of the division of neurosurgery at the State University of Iowa College of Medicine, urged medical educators to recognize that "the motivation of the student is as much the responsibility of the educator as that of providing course content and materiels." New experimental programs based on training of the individual mind, interdepartmental teaching, resident clinical clerkships, the family physician approach, and preventive medicine were described, respectively, by Dr. George T. Harrell, dean of the University of Florida School of Medicine; Dr. John L. Caughey, associate dean of Western Reserve University School of Medicine; Dr. Ralph E. Snyder, dean of New York Medical College; Dr. Louis F. Rittelmeyer Jr., associate professor of preventive medicine and director of the section on general practice at the University of Mississippi School of Medicine; and Dr. William L. Fleming, professor of preventive medicine at the University of North Carolina School of Medicine.

Dr. Harvey B. Stone, associate professor of surgery (emeritus) at Johns Hopkins University School of Medicine and former member of the A. M. A. Council on Medical Education and Hospitals, read a paper on "Filling the Gap Between Academic Medicine and Practice." He made the following suggestions. 1. Schools that employ only full-time teachers should abandon that system and bring part-time practicing physicians into their faculties. 2. The schools should give a warmer welcome to their part-time teachers with respect to rank, prestige, and voice in policy. 3. University hospitals should abandon the intern year and medical school graduates should serve their internships in nonuniversity hospitals. Dr. H. G. Weiskotten, Chairman of the Council on Medical Education and Hospitals, presented Dr. Stone with a scroll honoring him for his many years of service to the Council.

Dr. Elmer Hess, A. M. A. President, who addressed the federation dinner, emphasized that the main objective of medical education should be "the training of the physician as a whole man." Dr. Weiskotten told the congress that there has been a substantial increase in the number of specialists entering practice in smaller communities. His latest survey of medical school graduates shows that the proportion of specialists practicing in communities under 50,000 population has increased from 26% of the 1935 graduates who specialized to 35.4% of the 1945 graduates who chose specialties. Dr. Weiskotten reported that the proportion of graduates entering general practice has remained fairly steady over the past 30 years, while there has been a sharp decrease in the proportion of graduates becoming general practitioners with particular attention to a specialty.

FOUNDATION AWARDS TEN PRACTICE GRANTS

Assistance in the establishment of 10 medical practice units ranging from $3,000 to $25,000 has been announced by the Sears-Roebuck Foundation, Chicago. These grants were made under the 1955 plan of assistance which the Sears-Roebuck Foundation introduced last year (THE JOURNAL, Sept. 3, 1955, page 38). The foundation grants long-term, unsecured loans to physicians to enable them to complete the financing of their practices. The foundation administers the plan, while the screening and selection of applicants is done by a 17-member advisory board of leading physicians from all sections of the country named by the Board of Trustees of the American Medical Association. In announcing the 10 grants, the foundation said it has allotted $125,000 for the plan during 1956. This amount, plus $24,000 remaining from the 1955 budget, will make a minimum of $149,000 available for the coming year.

Loans last year went to 18 doctors who are setting up 10 practice units in eight states. The units fall into two categories: those that bring medical care and facilities to communities where none exist and those that retain existing care and facilities in communities about to lose them. Eight are being established in small towns in northern Georgia, central and northeast Oklahoma, southwest Colorado, northern Texas, southwest Michigan, southeast New York, and Connecticut. The others are in suburbs of Tulsa, Okla., and Seattle.

Theodore V. Houser, president of the Sears-Roebuck Foundation, said that he felt the plan had progressed satisfactorily in its initial phase, but in the future greater emphasis would be placed on helping locate doctors in communities without medical care. Mr. Houser said, "Some of the criteria for evaluating requests for assistance will be the professional qualifications of the applicant, the availability of medical service in the community, the extent of community participation in establishing the proposed unit, and the soundness of the plans proposed for providing medical care."

The Sears-Roebuck Foundation plan of assistance program began early in 1955 with the publication of a detailed booklet, "A Planning Guide for Establishment of Medical Practice Units." Copies of the booklet, designed to aid doctors in planning new medical facilities and converting and enlarging existing units, were furnished to state medical socieites, hospitals, and medical schools. In September, 1955, the foundation announced its financial plan of assistance. These loans are granted only when the physicians have utilized all conventional loan facilities and serve to make up the difference between conventional financing and completed cost. Loans are not made for the purpose of refinancing current obligations, Mr. Houser said.

Grants are repayable any time within 10 years, with payments being made in equal monthly installments starting not later than the beginning of the fourth year. Until repayment is begun, interest is charged at the rate of 6% a year, payable monthly. No further interest is charged after repayment begins. After the fifth year when interest payments have ceased, recipients make monthly contributions to a revolving fund. This is in recognition

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of the aid they have received and to assist other physicians. All interest and pledge money, along with all repaid loans, is used for the purpose of establishing additional medical practices. The addition of these funds to the basic amounts provided by the Sears-Roebuck Foundation will enable the plan to grow, Mr. Houser said. Specific information about the plan may be obtained from state medical associations or the Council on Medical Service of the American Medical Association.

BLOOD COUNCIL RECEIVES PRESIDENTIAL ENCOURAGEMENT

Dr. Leonard W. Larson, Bismarck, N. D., president of the Joint Blood Council, has made public a letter from President Eisenhower encouraging the newly formed national organization to develop a coordinated nationwide blood service, for peacetime as well as in emergencies. President Eisenhower praised the program and said that its five member organizations "in voluntarily forming a council to coordinate blood banking facilities have made an important contribution to the welfare of our country." Member institutions of the council are the American National Red Cross, the American Association of Blood Banks, the American Hospital Association, the American Medical Association, and the American Society of Clinical Pathologists.

The texts of the President's letter and Dr. Larson's letter of acknowledgment follow.

January 27, 1956

Dear Doctor Larson:

The newly formed Joint Blood Council has embarked upon a program of significant importance to all Americans. The many problems involved in bringing together on a cooperative basis the blood banking facilities of the country is a humanitarian effort in keeping with the American tradition.

Our people need a nationwide blood service, coordinated not only to take care of national emergencies, but to make available to them in time of peace the blood and its derivatives necessary to save life wherever the requirement may arise.

The American National Red Cross, the American Association of Blood Banks, the American Hospital Association, the American Medical Association, and the American Society of Clinical Pathologists in voluntarily forming a council to coordinate blood banking facilities have made an important contribution to the welfare of our country.

Sincerely,
DWIGHT D. EISENHOWER.

Dr. Leonard W. Larson
President
Joint Blood Council, Inc.
1832 M Street, N. W.
Washington 6, D. C.

February 14, 1956

The Honorable Dwight D. Eisenhower
The White House
Washington, D. C.

Dear Mr. President:

The officers and Board of Directors of the Joint Blood Council are highly pleased and honored by your letter of January 27, 1956.

Our program will be directed toward developing ways and means to make blood and its derivatives available to all persons in the United States. Also we plan to work in harmony with all blood banking and research facilities, both governmental and private, in establishing a uniform system of technical and administrative procedures which will advance the scientific application of blood for better health.

In keeping with the traditions of the medical profession, and of our American methods of accomplishment, we are sincerely confident that this new Council will render great service to our country in times of peace and emergency.

Your encouragement is deeply appreciated.

Very respectfully yours,
LEONARD W. LARSON, M.D.

At a recent meeting the council's board of directors took these actions: (1) decided to consider the development of a nationwide survey of blood banking institutions, with the possibility of maintaining a directory of blood banks describing their organization, location, facilities, and extent of service, and (2) announced formation of its scientific committee, whose members are Dr. Max M. Strumia, Bryn Mawr, Pa., chairman; Dr. Sam T. Gibson, American National Red Cross, Washington, D. C.; Dr. Morten Grove-Rasmussen, Massachusetts General Hospital, Boston; Dr. Elmer Jennings, Woman's Hospital, Detroit; Dr. William G. Workman, National Institutes of Health, Bethesda, Md.; and Dr. Frank E. Wilson, Washington, D. C., ex officio member.

The council said the committee's functions would be to (1) develop minimum standards for voluntary accreditation of blood banks; (2) develop ideal standards or methods in blood bank procedures, which will insure safe blood for the recipient; (3) study and make recommendations on new research developments and advise on their possible application in routine blood bank work; (4) explore ways and means of stimulating the development of facilities for studying unusual serum and red blood cells and for making them available; (5) advise, when requested, concerning the expansion of existing blood bank facilities in the event of a local or national disaster; (6) serve on request as an advisory body to the National Institutes of Health and other federal agencies on research and developments in the field of blood banking; and (7) recommend other pertinent scientific investigations for consideration by the board of directors.

The council established its office in Washington, D. C., last Nov. 1 and has as its officers Drs. Larson; James J. Griffitts, Miami, Fla., vice-president; Frank E. Wilson, executive vice-president; and Karl S. Klicka, Chicago, treasurer.

MEDICAL FILMS

The Committee on Medical Motion Pictures announces that booklet no. 7 of Reviews of Medical Motion Pictures is now ready for distribution. This booklet contains 83 critical reviews of medical and health films that were published in THE JOURNAL during 1955. A copy has been sent to the secretary of each state medical society, and copies are available to county medical societies upon request to the Committee. Other requests will be filled by the Order Department upon receipt of 25 cents for booklet no. 7 or $1 for the complete set of seven booklets, including all reviews published since 1946.

MEDICAL NEWS

CALIFORNIA

Nathanson Lectures.—Dr. J. H. Burn, department of pharmacology, Oxford University, England, will deliver the Morris Henry Nathanson Memorial Lectures at the University of Southern California, Los Angeles, March 19, 21, and 23 at Founders Hall. The lectures, which will begin at 8 p. m., will concern "Cardiac Enzymes." On March 21 Dr. Burn will speak at Los Angeles County General Hospital at 11 a. m.

Home Care Program.—The first few patients have been admitted at Mount Zion Hospital to the San Francisco Home Care Program, a demonstration and research program covering all types of chronic diseases and all ages. The program will admit patients from all hospitals and agencies in the city as well as those referred by private physicians. Dr. Edgar J. Munter is medical director, Mr. Mark Berke, hospital director, is director of the program, and Dr. Richard Baron, San Francisco, is the first physician on the program's visiting staff. Two or three physicians eventually will be needed on the visiting staff, and in addition all medical, surgical, and psychiatric disciplines will be called on. For information, call Miss Alice Gonnerman, Coordinator (telephone, Ext. 258-259).

CONNECTICUT

Lectures on Rehabilitation.—The rehabilitation study unit, Yale University School of Medicine, New Haven, presented "Physical Treatment in Cerebrovascular Accident" by Dr. Robcliff V. Jones Jr., assistant director, physical medicine and rehabilitation, March 7. At 4 p. m., March 21, in the Trask Room, "Physical Disabilities in Children" will be discussed by Dr. Thomas F. Hines, director, physical medicine and rehabilitation, and, on April 4 at the same time and place, "Electromyography" will be the topic of Dr. Sidney Licht, of the Veterans Administration Hospital at West Haven.

DISTRICT OF COLUMBIA

Kober Lecture.—Dr. Harry S. Bernton, professor of hygiene and preventive medicine, Georgetown University School of Medicine, Washington, D. C., will give the Kober Lecture March 21 in Gaston Hall at Georgetown Medical Center, where the late Dr. George M. Kober, who endowed the lecture, was dean for many years. Dr. Bernton, who succeeded Dr. Kober when the latter became professor emeritus, will discuss "The Clinical and Biochemical Aspects of Allergy."

ILLINOIS

Clinics for Crippled Children.—The University of Illinois division of services for crippled children has scheduled the following clinics to which any private physician may refer or bring children for consultative services:

March 20, Shelbyville, Methodist Church.
March 21, Evergreen Park, Little Company of Mary Hospital.
March 21, Springfield (cerebral palsy), Memorial Hospital.

Personal.—Dr. John H. Rendok, Springfield, has been appointed consultant in maternity, bureau of maternal and child health, state department of public health. For the past nine years Dr. Rendok has been in private practice in Springfield, where he served on the attending staffs of Memorial and St. John's hospitals. He was previously associated with the state department of public health.——Dr. Louis Ostrom, Rock Island, recently announced his intention to retire, after more than 54 years in practice. Dr. Ostrom, who is 81 years old, served in the Medical Corps overseas in World War I as a captain and a major. He is a past-president of the Rock Island County Medical Society and the medical and surgical staff at St. Anthony's Hospital. He has long been active also in civic affairs in Rock Island.

Chicago

School Named for Dr. Hess.—Chicago's newest school, located at 3500 Douglas Blvd., has been named after the late Dr. Julius Hays Hess, who died last November. The school, which has taken over the building formerly occupied by the Jewish Peoples Institute, is the first to serve only seventh and eighth grade pupils.

Dr. William Fishbein Resigns.—Dr. William I. Fishbein, epidemiologist in the Chicago Health Department since 1937, has announced his resignation. He will become medical consultant to an eastern manufacturer of low-calorie foods. Dr. Fishbein, who served as director of health surveys with the health department from 1925 to 1927, was associated with the health section of the sanitary district from 1927 to 1931, after which he returned to the health department as director of maternal and infant welfare.

Special Joint Ophthalmologic Meeting.—The Chicago Ophthalmological Society and the National Society for the Prevention of Blindness will hold a joint meeting March 26 at Stouffer's Restaurant in the Prudential Building, 32 E. Randolph St. (telephone STate 2-3711). A cocktail hour, 6 p. m., at the Top-of-the-Rock, will precede dinner, on the ground floor (dinner, $3.75; wives welcome; early reservations necessary; no cancellations after noon on March 22). At 8 p. m. Dr. Derrick T. Vail will present "Ophthalmology and the Illinois Society for the Prevention of Blindness," after which "The Nationwide Fight Against Blindness" will be considered by Dr. Franklin M. Foote, New York City, executive director of the National Society for the Prevention of Blindness. There will be no instruction hour or clinical meeting, as this is a special meeting replacing the regular monthly meeting of the society.

INDIANA

Society News.—At the County Society Officers Conference at the Hotel Lincoln, Indianapolis, March 18, the Indiana State Medical Association will present Mr. Leo E. Brown, Chicago, Director, Public Relations Department, American Medical Association, who will discuss "What Your Patients Say About You."

Psychiatric Seminar.—The third annual postgraduate seminar in psychiatry for physicians in general practice and nonpsychiatric specialties has been scheduled for March 28, April 4, and April 11 under the sponsorship of the committee on medical education and hospitals of the Indiana State Medical Association. The seminar "Psychiatry in Your Daily Practice" will be held in the auditorium of the Child Guidance Clinic of Marion County from 10:30 a. m. to 8 p. m. Information may be obtained from: Psychiatric Seminar, Norways Foundation Hospital, 1800 E. 10th St., Indianapolis 1.

Surgical Meeting.—The annual meeting of the Indiana division, International College of Surgeons, will be held March 21 in the Clinic Building auditorium at Indiana University School of Medicine, Indianapolis, under the presidency of Dr. Emmett B. Lamb, Indianapolis. All physicians are invited. There is no registration fee. The program will open at 10 a. m. with a two-hour wet clinic. After luncheon (12 noon-1:30 p. m.) in the Student Union Building, the following program, preceded by a surgical film, will be presented:

Alfred H. Whittaker, Detroit, Emergency Treatment for the seriously Injured.
John DeJ. Pemberton, Mayo Clinic, Rochester, Minn., Nodules of the Thyroid Gland, Their Significance and Management.
Chester C. Guy, Chicago, Present Status of Surgery for Duodenal Ulcer.

Dr. Dwight H. Murray, Napa, Calif., President-Elect of the American Medical Association, will be the speaker at the banquet, 7 p. m. at the Claypool Hotel, which will be preceded by a cocktail hour.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

IOWA

Society News.—Dr. Gunnar Heuser, University of Montreal (Canada) Institute of Experimental Medicine and Surgery, will be the guest speaker at the meeting of the Polk County Medical Society in Des Moines, March 21, when he will talk on stress.

County Medical Centennial.—The Scott County Medical Society of Iowa will hold its centennial March 21 at the Blackhawk Hotel in Davenport. The program in the afternoon will be featured by papers, "Recent Setbacks in Medicine" by Dr. William B. Bean of Iowa City, "The Spread of Tumors" by Dr. William Boyd, professor of pathology, University of Toronto (Canada) Faculty of Medicine, and "Progress in Stress Research" by Dr. Andre Robert of Montreal, Canada. At 6 p. m. a social hour will precede the banquet, after which an address will be given by Dr. Elmer Hess, Erie, Pa., President of the American Medical Association. Dr. Walter L. Bierring, Des Moines, a Past-President of the American Medical Association, will then give "The History of Scott County Medicine." Interested physicians are invited. Reservations for the luncheon and banquet may be made through Dr. James F. Bishop, 1818 Harrison St., Davenport.

LOUISIANA

Conference on Handicapped Children.—A statewide conference on handicapped children will be held March 23-24 at the Louisiana State University, New Orleans, under the sponsorship of the Governor's Committee on Handicapped Children. Eugene J. Taylor, B.S. (Educ.), A.M., assistant professor of clinical medicine and rehabilitation, New York University College of Medicine, will address the conference on the problem of personnel. Mr. Taylor is a member of the subcommittee on paramedical personnel of the National Health Resources Advisory Committee. The conference climaxes more than a year's work by the governor's committee, which included a study of public and voluntary agencies engaged in serving handicapped children. The project is being supported, in part, by the Nemours Foundation for Crippled Children, Wilmington, Del.

MAINE

Tuberculosis in Childhood.—A symposium on tuberculosis in childhood will be presented at the Central Maine Sanitarium, Fairfield, March 18, under the sponsorship of the Maine Department of Health and Welfare and the Maine Trudeau Society. Dr. Edith H. Lincoln, professor of clinical pediatrics, New York University College of Medicine, will conduct the program, which will begin with her presentation of "Pathogenesis of Tuberculosis and Clinical Pictures." Dr. Charlotte Marker, assistant professor of pediatrics, New York University College of Medicine, will discuss "Laboratory Diagnosis" and Dr. Pamela Davies, research fellow, "Case Findings, Tuberculin Tests, and BCG." "Indications and Methods of Treatment" will be given by Drs. Lincoln, Marker, and Davies, after which Dr. Marker will present "Psychological Care" and Dr. Davies "Educational and Recreational Needs and Rehabilitation."

MICHIGAN

Gudakunst Memorial Lecture.—The seventh annual Don W. Gudakunst Memorial Lecture will be delivered at the School of Public Health, University of Michigan, Ann Arbor, March 20, 4 p. m. Dr. Thomas Francis Jr., University of Michigan, will present "Approaches to the Prevention of Poliomyelitis."

MINNESOTA

Memorial Fund.—The late Drs. S. H. Boyer Sr. and Robert L. Nelson are the first two persons memorialized in a fund established at St. Luke's Hospital, Duluth, to honor deceased physicians. Donations will be used to purchase equipment for the medical staff, especially in the field of interest of the physician being honored.

Society News.—At the meeting of the Ramsey County Medical Society in St. Paul, March 26, Dr. David P. Boyd of the Lahey Clinic, Boston, and Dr. Andrew L. Banyai of Marquette University School of Medicine, Milwaukee, will collaborate in a panel on bronchiogenic carcinoma, for which Dr. Herman J. Moersch of the Mayo Clinic, Rochester, will serve as moderator.

NEW YORK

Vander Veer Memorial Lecture.—On March 21, 8:30 p. m., the Albany Medical College chapter of Nu Sigma Nu will present its annual Albert Vander Veer Memorial Lecture in the auditorium of the Albany Law School. Dr. Charles B. Huggins, University of Chicago School of Medicine, will discuss "Endocrine Effects on Mammary Cancer." All physicians in the Albany area are cordially invited.

Symposium on Cancer.—At its meeting in Brooklyn March 19, the Ocean Medical Society will present a symposium on cancer by Dr. Richard D. Brasfield, New York City (Management of Tumors of the Colon), Dr. Irving M. Ariel, New York City (Management of Cancer of the Rectum), and Dr. George T. Pack, New York City (The Diagnosis and Treatment of Metastatic Cancer of the Liver).

Symposium on Occupational Disease.—A symposium on occupational disease, planned especially for general practitioners and industrial medical personnel, will be held March 22 at the Medical Society of the County of Queens, 112-25 Queens Blvd., Forest Hills. The symposium, which is approved by the American Academy of General Practice for formal credit, will be presented at 2 p. m. and at 8 p. m. For information, call Miss Charlotte von der Heyde, 159-29 90th Ave., Jamaica (JAmaica 6-2557).

Lecture by Dr. Priscilla White.—The Syracuse chapter of Alpha Epsilon Iota will sponsor a lecture on "Diabetes in Pregnancy" by Dr. Priscilla White at 8:30 p. m., March 20, in the auditorium of the State University of New York College of Medicine at Syracuse. Dr. White is a member of the Joslin Clinic, attending physician at New England Deaconess, Boston Lying-in, and Faulkner hospitals, Boston, and an instructor in pediatrics at her alma mater, Tufts College Medical School, Boston. Physicians and medical students are invited.

Society News.—On March 20, in the McNaughton Auditorium, Brooklyn, the Medical Society of the County of Kings and Academy of Medicine of Brooklyn will hear Dr. Max L. Rosenheim, professor of medicine, University of London, discuss "The Management of Hypertension."——At the meeting of the Nassau Neuropsychiatric Society March 20, 9 p. m., at the Meadowbrook Hospital, Hempstead, Dr. Giorgio Lolli, research associate in applied physiology at Yale University, New Haven, Conn., will present a paper on "Alcoholism and Obesity, Both Problems of Hunger." Dr. Lolli is associate editor of the *Quarterly Journal of Studies on Alcohol* and director of the Silkworth Memorial Service, Knickerbocker Hospital, New York City.

New York City

Society News.—The Bronx Society of Neurology and Psychiatry will meet at the Veterans Administration Hospital, 3A conference room, 130 W. Kingsbridge Rd., Bronx, March 22, at 8:30 p. m. "Traumatic and Nontraumatic Intracranial Hemorrhages" will be discussed by Dr. Milton Helpern, chief medical examiner, New York City.

Pollitzer Lecture.—Dr. Walter B. Shelley, associate professor of dermatology, University of Pennsylvania School of Medicine, Philadelphia, will give the sixth annual Sigmund Pollitzer Lecture on "Recent Studies on the Physiology and Biochemistry of Itching" in the Psychiatric Amphitheatre of Bellevue Hospital, 400 E. 30th St., March 19, 4 p. m.

Seminars on History of Surgery.—On March 21, 8:30 p. m., Mount Sinai Hospital (Fifth Avenue and One Hundredth Street) will present the fifth seminar meeting on the history of surgery in conference room P in the basement of the Guggenheim Pavilion. Guests are invited. "Ophthalmology in the Middle Ages" will be considered by Harry H. Sobotka, Ph.D.

Ross Golden Lecture.—The third Ross Golden Lecture, "Can We Afford Photofluorography?" will be given by Dr. W. Edward Chamberlain, professor of radiology, Temple University School of Medicine, Philadelphia, at the New York Academy of Medicine, March 19, 8 p. m., under the joint sponsorship of Columbia University and the New York Roentgen Society.

NORTH CAROLINA

Cancer Symposium.—The Forsyth County Cancer Symposium will have its fifth annual program March 29 in the Robert E. Lee Hotel in Winston-Salem. The symposium, which is concerned with tumors of the urinary tract in relation to other systems, will consist of four papers and a panel discussion. A social hour will follow the afternoon session, and in the evening there will be a dinner meeting. Physicians and their wives are invited to attend the dinner as guests of the Forsyth County Medical Society.

OHIO

Society News.—On March 21, 8 p. m., at the Cincinnati Sanitarium, 5642 Hamilton Ave., the Cincinnati Society of Neurology and Psychiatry will present Dr. Seymour S. Kety, director of research, National Institutes of Mental Health and Neurological Diseases and Blindness, Bethesda, Md., who will consider "The Circulation and Metabolism of the Human Brain."

History of Academy Televised.—The Academy of Medicine of Cincinnati is staging a series of television shows over Cincinnati's educational station, WCET. The 13-week series will tell the history of the academy and reveal how it operates to the benefit of the community. Dr. Joseph E. Ghory is technical advisor for the series. Dr. Charles A. Sebastian, president of the academy, and Mr. Edward Willenborg, executive secretary, appeared on the first program.

Visiting Lecturer.—Dr. H. Russell Meyers, chairman, division of neurosurgery, University Hospitals, Iowa City, will serve as visiting professor of neurology at the Cincinnati General Hospital, March 21-24. He will partake in ward rounds, conferences, and teaching sessions and will deliver the following lectures in the Mont Reid Pavilion:

March 21, 11 a.m.: An anthropologic view of current-day neurology.

March 22, 11 a.m.: Traditional scientific method and Aristotelian logic in modern medicine.

March 23, 11 a.m.: Plato's theory of form. Cannon's concept of homeostasis and biologic "drives."

March 23, 11:30 a.m.: The neurologist's potential for creativeness.

Course on Isotopes.—"Isotopes in Clinical Medicine" is the subject of a course that will be presented March 19-24 and March 26-31 at the Ohio State University Hospital, Columbus, under the auspices of the American College of Physicians and the direction of Drs. Charles A. Doan, William G. Myers, and Bruce K. Wiseman. One week is outlined for physicians interested in orientation and techniques in applying radioactive isotopes in tracer and therapeutic dosages in clinical medicine. During a second elective week, practical individual laboratory exercises will supplement the demonstrations of the first week. This program will be designed for a limited number of the physicians attending the first week who may desire to gain more extensive practical experience in making measurements with, and in the administration of, some of the radioisotopes.

VIRGINIA

Stoneburner Lectures.—The annual Stoneburner Lectures will be delivered at the Medical College of Virginia, Richmond, March 21 and 22, by Dr. Ernest W. Goodpasture, scientific director, department of pathology, Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D. C. These evening lectures will follow the day-time presentation of a symposium on clinical pathology.

Medicolegal Workshop.—The department of legal medicine of the Medical College of Virginia, Richmond, the chief medical examiner's office, and the Virginia Society of Pathology and Laboratory Medicine are sponsoring a medicolegal workshop for medical examiners, pathologists, and other interested physicians, March 23, 8 a. m.-4:30 p. m., at the college. The medical examiners will have a joint session with the pathologists, in which obscure causes of death and special techniques will be discussed. The pathologists will have an opportunity to witness procedures and techniques of medicolegal autopsies. Registration is limited. For information address Dr. Geoffrey T. Mann, Chairman, Department of Legal Medicine, Medical College of Virginia, Richmond.

Postgraduate Day.—The staff of the Roanoke Memorial Hospital invites physicians of Roanoke and the southwest Virginia area to attend its seventh annual Postgraduate Day Program March 21 at the Hotel Roanoke. The program will open at 2 p. m. with "Bronchography and Abdominal Aortography" by Dr. Benjamin Felson, professor and chairman, department of radiology, Cincinnati General Hospital and University of Cincinnati School of Medicine, after which a clinical-pathological conference will be presented by Dr. Thomas H. Hunter, dean and professor of medicine, and Dr. David E. Smith, professor of pathology, University of Virginia School of Medicine, Charlottesville. At 3:45 p. m. Dr. David M. Hume, Peter Bent Brigham Hospital, Boston, will serve as moderator for a panel discussion, "Gallbladder Disease," with Drs. Felson, Hunter, and Smith as collaborators. Following the afternoon session, there will be a social hour and banquet. At 7:30 p. m. "Use of Steroids in Surgical Practice" will be considered by Dr. Hume.

WEST VIRGINIA

Meeting of Pediatricians.—The West Virginia Pediatric Society will meet at the Waldo Hotel in Clarksburg, March 22. The following program will be presented at 1:30 p. m. by faculty members of the University of Pittsburgh School of Medicine:

Neurological Problems of Infancy Amenable to Surgery, Anthony F. Susen, clinical instructor in neurosurgery.

Pathological Bleeding States in Childhood, Paul C. Gaffney, associate professor of pediatrics.

Bony Lesions Seen in a Pediatrician's Office, Thomas D. Brower, assistant professor of orthopedics.

Physicians in West Virginia are invited to attend the meeting, which will be adjourned at 4:30 p. m.

WISCONSIN

Personal.—Dr. David W. Barrow, professor of surgery at Marquette University School of Medicine, Milwaukee, and director for postgraduate clinics at Milwaukee County Hospital, has been appointed assistant director of surgery at the hospital.

Community Health Week.—Observance of National Community Health Week, March 18-24, will be marked in Milwaukee by a promotion campaign for the poison control project, under joint sponsorship of the Medical Society of Milwaukee County and the Milwaukee Junior Chamber of Commerce. The medical society and the Jaycees and Jaycettes plan to distribute (1) literature explaining the poison control centers and how parents can utilize their facilities, (2) first-aid charts, suitable for mounting on the inside of home medicine cabinets, which give information for treatment in accidental poisoning, and (3) large display cards telling of the promotion of the project. Information concerning the Milwaukee plan may be obtained from the Medical Society of Milwaukee County, 208 E. Wisconsin Ave., Milwaukee 2.

HAWAII

Society News.—A regional meeting of the American College of Physicians of Hawaii was held March 6 to honor its president, Dr. George F. Strong of Vancouver, Canada. The following presentations were made:

Lieut. Col. Edwin J. Pulaski, Washington, D. C., V-Cillin.

Col. Ogden C. Bruton, Washington, D. C., A-Gammaglobulemia.

Major Edwin S. Stenberg, Denver, Cortisone in the Treatment of "Mumps" Orchitis.

Major Chapel E. Carter, Problems of Air Evacuation of Patients in the Pacific.

A panel discussion, "Dangers in the Use of Steroids," had as moderator Dr. Harry L. Arnold Sr., Honolulu, and as collaborators Drs. Thomas Sweetmin, John L. Bell, Samuel D. Allison, and Morton E. Berk, Honolulu. A round-table discussion was held on cardiovascular disease.

GENERAL

Meeting of Surgeons.—The annual regional meeting of the southern California division and of the northern California chapter of the International College of Surgeons will be held at the St. Claire Hotel, San Jose, Calif., March 22-23. Members and families of the medical and allied professions are invited to attend. Communications should be addressed to Dr. Carmelo C. Celestre, 1686 Union St., San Francisco 3, or to Dr. Ross V. Parks, 1930 Wilshire Blvd., Los Angeles 57.

Meeting of Neurosurgical Society.—The annual meeting of the Southern Neurosurgical Society will convene at the George Washington Hotel, Jacksonville, Fla., March 23-24. Introductory remarks at 9:20 a. m. Friday by Dr. James G. Galbraith, Birmingham, Ala., president, will be followed by "Anterior Choroidal Artery Occlusion for Parkinson's Disease" by Dr. Edward J. Sullivan (by invitation) and Dr. James G. Lyerly, Jacksonville, and "Electroencephalography in Neurological Diagnosis" by Dr. William H. McCullagh (by invitation) and Dr. William Ingram Jr. (by invitation), Jacksonville. Other presentations by invitation include: "Fibrous Dysplasia Without Systemic Skeletal Involvement" by Dr. Fleming L. Jolley, Atlanta, Ga., and "Phrenicofacial Anastomosis" by Dr. Robert C. Hardy, San Antonio, Texas, both of which will be delivered Saturday morning. On Friday, cocktails at 6:30 p. m. will precede the annual banquet.

Meeting of Psychosomatic Society.—The American Psychosomatic Society will hold its 13th annual meeting at the Sheraton Plaza Hotel, Boston, March 24-25. The Saturday morning session will be devoted to contributions from psychoanalysis and the Saturday afternoon session to contributions from sociology. The program will open at 9 a. m. Saturday with introduction of the chairman, Dr. Felix Deutsch, Boston, who will deliver "Reflections on Freud's 100th Birthday." Dr. Stanley Cobb, Boston, will deliver the presidential address at 2 p. m. The traditional pay-as-you-go cocktail party is scheduled for Saturday at 5 p. m. The Sunday afternoon program (members only) will be held at the Physiology Amphitheatre of Harvard Medical School. Dr. Carl A. Binger, Boston, will serve as chairman for this session, "Contributions from Neurophysiology," which will memorialize the late Dr. Walter B. Cannon. Registration fee for nonmembers of the society is $5, for students, interns, residents, and fellows, $1.

Conference on Human Nutrition.—The New England Conference on Human Nutrition will be held at the Hotel Sheraton Plaza, Boston, March 22-23 under the sponsorship of the Florida Citrus Commission. George R. Cowgill, Ph.D., professor of nutrition, Yale University School of Medicine, New Haven, Conn., will serve as moderator for the Thursday afternoon meeting, the theme of which will be "The Extent and Impact of the Nutrition Problem in the United States." The afternoon session will end with a panel discussion on nutritional problems in New England. Louis G. McDowell, Ph.D., Lakeland, Fla., director of research, Florida Citrus Commission, will be master of ceremonies at the banquet, 7:30 p. m., at which M. F. Ashley Montagu, Ph.D., Princeton, N. J., will discuss "Nature, Nurture and Nutrition." The theme of the Friday morning discussions will be "Nutrition Requirements Among the Population." The afternoon session will be devoted to a panel, "Putting Nutrition Information to Work."

Postgraduate Courses Not Previously Published.—Notification of the following courses has recently been received:

The American College of Physicians' course entitled "Recent Advances in Diagnosis and Treatment of the Heart," originally listed as a two-day course, will be a five-day course, March 19-23. It will consist of small group seminars, short didactic lectures, informal panel groups, and color television on a large screen to present new advances in **cardiology.** Registration for both members and nonmembers of the college must be handled directly through the Philadelphia office, 4200 Pine St., Philadelphia 4. The course will be presented at the University of Kansas Medical Center, Kansas City.

The course on **venereal disease** sponsored annually by the Department of Health, Education, and Welfare, Public Health Service, will be offered March 19-23 at the University of Washington School of Medicine, Seattle. This 30-hour lecture and discussion period course has no tuition fee because the costs are being borne by the Public Health Service. The enrollment will be unlimited.

A course on **fractures,** which began March 15, will be presented each Thursday afternoon (except April 5) for five lectures at the Rochester General Hospital, Rochester, New York (registration fee $15). The lecture series will have a minimum enrollment of 25 and a maximum of 50 physicians. Procedures in the treatment of common fractures, difficulties that usually arise, and means of avoiding them will be the subjects for lectures and demonstration.

A course, "The General Practitioner and **Anesthesia,**" will be presented May 16-18 at the Rochester General Hospital, Rochester, N. Y. (registration fee $10). This course is limited to 12 registrants.

A refresher course, "Pediatric Advances for Pediatricians and General Practitioners," will be offered May 28-June 1 by the staff of the Children's Hospital of Philadelphia in collaboration with the department of **pediatrics** of the University of Pennsylvania School of Medicine and the Camden (N. J.) Municipal Hospital for Contagious Diseases. Tuition will be $100. For information, address the Children's Hospital of Philadelphia, 1740 Bainbridge St., Philadelphia 46.

FOREIGN

British Journal Celebrates Golden Jubilee.—The January issue of the *British Journal of Tuberculosis and Diseases of the Chest,* its golden jubilee number, contains articles on administrative antituberculosis work, tuberculosis control, clinical aspects of tuberculosis and diseases of the chest, progress in thoracic surgery, surgery of the heart and circulation, and other aspects of 50 years of progress. A jubilee celebration dinner was held Jan. 24 at the Claridge Hotel in London.

Health Congress.—The Royal Society of Health (formerly the Royal Sanitary Institute) announces the Health Congress at Blackpool, England, April 24-27. The topics will include: public health practice; new horizons in animal-human health relationships; mental health aspects of school children; control of yaws; prevention of accidents in the home; problems of river pollution in industrial areas; health hazards from atomic radiation; radiation, genetics and its human implications; travel and health; and high altiude and space travel.

Seminar Congresses in Radiology.—In its seminar congresses in radiology, the American Medical Society of Vienna will present the following programs by the medical faculty of the University of Vienna:

May 26-28, Diagnosis with Selected Practical Demonstrations
July 28-30, Therapy with Selected Practical Demonstrations.
Sept. 28-30, General Radiology with Selected Practical Demonstrations.
Nov. 24-26, Practical Demonstrations in Diagnosis and Therapy.

Details may be obtained from the American Medical Society of Vienna, Vienna I, Universitaetsstrasse 11, Cable: "Ammedic," Vienna.

DEATHS IN OTHER COUNTRIES

René Leriche, M.D., Hon. F.R.C.S., Hon. F.R.C.S.E., died Dec. 29, 1955, at Cassis, France, at the age of 76. After service in World War I, Dr. Leriche practiced in Lyons until 1924, when he was appointed professor of clinical surgery in the University of Strasbourg. In 1937 he accepted the position of Professeur au Collège de France. Since this position did not provide clinical facilities in any teaching hospital in Paris, for the remainder of his active years Dr. Leriche's clinical work was private and was done in his consulting rooms and in the American Hospital at Neuilly. The first volume of his professional lectures was "Surgery of Pain." Dr. Leriche was a member of the Institute in the French Academy of Sciences and a past-president of the International Society of Surgery. He was an honorary fellow of the Royal College of Surgeons of England, the Royal College of Edinburgh, Scotland, and the Royal Society of Medicine. In 1939 he was awarded the Lister medal.

CORRECTION

Treatment of Carbuncle.—In the Query and Minor Note entitled "Treatment of Carbuncle" in THE JOURNAL, Jan. 28, page 340, the sentence beginning in the 12th line of the answer should have read as follows: "A dose of one million units of crystalline penicillin dissolved in 5 cc. of saline solution to which is added 5 cc. of 2% procaine hydrochloride produces a solution containing 100,000 units of penicillin per cubic centimeter."

MEETINGS

AMERICAN MEDICAL ASSOCIATION: Dr. George F. Lull, 535 North Dearborn St., Chicago 10, Secretary.
1956 Annual Meeting, Chicago, June 11-15.
1956 Clinical Meeting, Seattle, Nov. 27-30.
1957 Annual Meeting, New York, June 3-7.
1957 Clinical Meeting, Philadelphia, Dec. 3-6.
1958 Annual Meeting, San Francisco, June 23-27.
1958 Clinical Meeting, Minneapolis, Dec. 2-5.

AERO MEDICAL ASSOCIATION, Drake Hotel, Chicago, Apr. 16-18. Dr. Thomas H. Sutherland, P. O. Box 26, Marion, Ohio, Secretary.

ALABAMA, MEDICAL ASSOCIATION OF THE STATE OF, Birmingham, Apr. 19-21. Dr. Douglas L. Cannon, 537 Dexter Ave., Montgomery, Secretary.

AMERICAN ACADEMY OF GENERAL PRACTICE, Hotel Statler, Washington, D. C., Mar. 19-22. Mr. Mac F. Cahal, Broadway at 34th Street, Kansas City 11, Mo., Executive Secretary.

AMERICAN ACADEMY OF NEUROLOGY, Hotel Jefferson, St. Louis, Apr. 23-28. Dr. Thomas W. Farmer, Dept. of Medicine, University of North Carolina, Chapel Hill, N. C., Secretary.

AMERICAN ACADEMY OF PEDIATRICS, Rice Hotel and Sam Houston Coliseum, Houston, Texas, Apr. 16-19. Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Illinois, Executive Secretary.

AMERICAN ASSOCIATION OF ANATOMISTS, Milwaukee, Apr. 4-6. Dr. Normand L. Hoerr, 2109 Adelbert Rd., Cleveland 6, Secretary.

AMERICAN ASSOCIATION FOR CLEFT PALATE REHABILITATION, Muehlebach Hotel, Kansas City, Mo., May 3-5. Dr. Richard C. Webster, 1101 Beacon Street, Brookline 46, Mass., Chairman, Program Committee.

AMERICAN ASSOCIATION FOR HEALTH, PHYSICAL EDUCATION, RECREATION, Conrad Hilton Hotel, Chicago, Mar. 24-30. Mr. Carl A. Troester Jr., 1201 Sixteenth St., N.W., Washington 6, D. C., Executive Secretary.

AMERICAN ASSOCIATION OF THE HISTORY OF MEDICINE, Washington Duke Hotel, Durham, N. C., Apr. 19-26. Dr. Ilza Veith, 950 East 59th St., Chicago 37, Executive Secretary.

AMERICAN ASSOCIATION OF IMMUNOLOGISTS, Chalfonte-Haddon Hall, Atlantic City, N. J., Apr. 16-20. Dr. F. S. Cheever, Univ. of Pittsburgh, School of Public Health, Pittsburgh 13, Secretary.

AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS, Netherland Plaza Hotel, Cincinnati, Apr. 26-28. Dr. Edward A. Gall, Dept. of Pathology, Cincinnati General Hospital, Cincinnati 29, Secretary.

AMERICAN ASSOCIATION OF RAILWAY SURGEONS, Drake Hotel, Chicago, Apr. 10-12. Dr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Secretary.

AMERICAN ASSOCIATION FOR THORACIC SURGERY, Fontainebleau Hotel, Miami Beach, Fla., May 7-9. Dr. Paul C. Samson, 3959 Happy Valley Road, Lafayette, Calif., Secretary.

AMERICAN COLLEGE OF ALLERGISTS, Hotel New Yorker, New York, Apr. 15-20. Dr. Fred W. Wittich, 401 Marquette Bank Bldg., Minneapolis 2, Secretary.

AMERICAN COLLEGE OF PHYSICIANS, Biltmore Hotel and Shrine Auditorium, Los Angeles, Apr. 16-20. Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Executive Secretary.

AMERICAN FEDERATION FOR CLINICAL RESEARCH, Chalfonte-Haddon Hall, Atlantic City, N. J., April 29. Dr. William W. Stead, VA Hospital, Minneapolis 17, Secretary.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION, Claridge Hotel, Atlantic City, N. J., Apr. 27-28. Dr. H. Marvin Pollard, University Hospital, Ann Arbor, Mich., Secretary.

AMERICAN GERIATRICS SOCIETY, Palmer House, Chicago, May 3-4. Dr. Malford W. Thewlis, 25 Mechanic St., Wakefield, R. I., Secretary.

AMERICAN GOITER ASSOCIATION, Drake Hotel, Chicago, May 3-5. Dr. John C. McClintock, 149½ Washington Ave., Albany 10, N. Y., Secretary.

AMERICAN OTOLOGICAL SOCIETY, Seigniory Club, P.Q., Canada, May 11-12. Dr. Laurence R. Boies, 90 South Ninth St., Minneapolis 2, Secretary.

AMERICAN PEDIATRIC SOCIETY, The Inn, Buck Hill Falls, Pa., May 6-11. Dr. Aims C. McGuinness, Memorial Hospital Association of Kentucky, 1427 I St., N.W., Washington 5, D. C., Secretary.

AMERICAN PHYSIOLOGICAL SOCIETY, Atlantic City, N. J., Apr. 16-20. Dr. Allan C. Burton, University of Western Ontario, London, Ontario, Canada, Secretary.

AMERICAN PSYCHIATRIC ASSOCIATION, Chicago, April 30-May 4. Dr. William Malamud, 80 East Concord St., Boston 18, Secretary.

AMERICAN PSYCHOSOMATIC SOCIETY, Sheraton Plaza, Boston, Mar. 24-25. Dr. Theodore Lidz, 333 Cedar St., New Haven 11, Conn., Secretary.

AMERICAN RADIUM SOCIETY, Shamrock Hotel, Houston, Texas, Apr. 9-11. Dr. Robert E. Fricke, 102 Second Ave. S.W., Rochester, Minn., Secretary.

AMERICAN SOCIETY FOR ARTIFICIAL INTERNAL ORGANS, Atlantic City, N. J., Apr. 15-16. Dr. Peter F. Salisbury, Institute for Medical Research, 4751 Fountain Ave., Los Angeles 29, Secretary.

AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, Chalfonte-Haddon Hall, Atlantic City, N. J., Apr. 15-19. Dr. Philip Handler, Duke University, Durham, N. C., Secretary.

AMERICAN SOCIETY FOR CLINICAL INVESTIGATION, Chalfonte-Haddon Hall, Atlantic City, N. J., April 30. Dr. J. D. Myers, University of Pittsburgh School of Medicine, Pittsburgh 13, Secretary.

AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY, Atlantic City, N. J., Apr. 15-21. Dr. Cyrus C. Erickson, 874 Union Ave., Memphis 3, Tenn., Secretary.

AMERICAN SOCIETY OF MAXILLOFACIAL SURGEONS, Jung Hotel, New Orleans, Mar. 18-21. Dr. John A. Drummond, 1414 Drummond St., Montreal, Canada, Secretary.

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, Atlantic City, N. J., Apr. 15-20. Dr. Carl C. Pfeiffer, Emory University School of Medicine, Emory University, Ga., Secretary.

AMERICAN SURGICAL ASSOCIATION, The Greenbrier, White Sulphur Springs, W. Va., Apr. 11-13. Dr. R. Kennedy Gilchrist, 59 East Madison St., Chicago 3, Secretary.

ARIZONA MEDICAL ASSOCIATION, San Marcos Hotel, Chandler, Apr. 25-28. Dr. D. W. Melick, 411 Security Bldg., Phoenix, Secretary.

ARKANSAS MEDICAL SOCIETY, Hotel Marion and Robinson Auditorium, Little Rock, Apr. 23-25. Mr. Paul C. Schaefer, 213 Kelley Bldg., Ft. Smith, Executive Secretary.

ASSOCIATION OF AMERICAN PHYSICIANS, Chalfonte-Haddon Hall, Atlantic City, N. J., May 1-2. Dr. Paul B. Beeson, Yale University School of Medicine, New Haven 11, Conn., Secretary.

ASSOCIATION OF AMERICAN PHYSICIANS AND SURGEONS, Columbus, Ohio, Apr. 5-7. Dr. William L. Baughn, 1635 West 25th St., Anderson, Ind., Secretary.

CALIFORNIA MEDICAL ASSOCIATION, Ambassador Hotel, Los Angeles, April 29-May 2. Mr. John Hunton, 450 Sutter St., San Francisco 8, Executive Secretary.

CONNECTICUT STATE MEDICAL SOCIETY, Hamden, Apr. 24-26. Dr. Creighton Barker, 160 St. Ronan St., New Haven, Executive Secretary.

EASTERN SECTION, AMERICAN CONGRESS OF PHYSICAL MEDICINE AND REHABILITATION, Hotel Adelphia, Philadelphia, April 7. Dr. Harold Lefkoe, 1006 Medical Tower, Philadelphia 3, Secretary.

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, Chalfonte-Haddon Hall, Atlantic City, N. J., Apr. 16-20. Mr. M. O. Lee, 2101 Constitution Ave., Washington 25, D. C., Secretary.

HAWAII MEDICAL ASSOCIATION, Reef Hotel, Honolulu, Apr. 22-29. Dr. William S. Ito, 510 S. Beretania St., Honolulu, Secretary.

INDUSTRIAL MEDICAL ASSOCIATION, Philadelphia, Apr. 23-26. Dr. H. Glenn Gardiner, Inland Steel Co., East Chicago, Ind., Secretary.

INTERNATIONAL ACADEMY OF PROCTOLOGY, Drake Hotel, Chicago, Apr. 23-26. Dr. Alfred J. Cantor, 43-55 Kissena Blvd., Flushing, N. Y., Secretary.

INTERSTATE ORTHOPEDIC SOCIETY, Pittsburgh, April 18. Dr. Harold H. Sankey, 121 University Place, Pittsburgh 13, Secretary.

IOWA STATE MEDICAL SOCIETY, Savery Hotel and Veterans Memorial Auditorium, Des Moines, Apr. 22-25. Mr. Donald L. Taylor, 529 36th St., Des Moines 12, Executive Secretary.

JOHN A. ANDREW CLINICAL SOCIETY, Memorial Hospital, Tuskegee Institute, Alabama, Apr. 8-13. Dr. Eugene H. Dibble Jr., John A. Andrew Memorial Hospital, Tuskegee Institute, Ala., Secretary.

KANSAS MEDICAL SOCIETY, Jayhawk Hotel, Topeka, April 29-May 3. Mr. Oliver E. Ebel, 315 West 4th St., Topeka, Executive Secretary.

LOUISIANA STATE MEDICAL SOCIETY, Hotel Bentley, Alexandria, Apr. 23-25. Dr. C. Grenes Cole, 1430 Tulane Ave., New Orleans 12, Secretary.

MARYLAND, MEDICAL AND CHIRURGICAL FACULTY OF THE STATE OF, BALTIMORE, May 2-4. Dr. Everett S. Diggs, 1211 Cathedral St., Baltimore 1, Secretary.

MICROCIRCULATORY CONFERENCE, Hotel Schroeder, Milwaukee, Apr. 3. Dr. George P. Fulton, Boston University, College of Liberal Arts, 725 Commonwealth Ave., Boston 15, Chairman.

MISSISSIPPI STATE MEDICAL ASSOCIATION, Hotel Heidelberg, Jackson, May 8-10. Mr. Rowland B. Kennedy, 860 Milner Bldg., Jackson, Executive Secretary.

MISSOURI STATE MEDICAL ASSOCIATION, Hotel Jefferson, St. Louis, Apr. 8-11. Dr. E. Royse Bohrer, 634 North Grand Blvd., St. Louis 3, Secretary.

NATIONAL SOCIETY FOR THE PREVENTION OF BLINDNESS, Palmer House, Chicago, Mar. 26-28. Dr. Franklin M. Foote, 1790 Broadway, New York 19, Executive Director.

NEW ENGLAND HEALTH EDUCATION ASSOCIATION, University of Connecticut, Storrs, Conn., May 11-12. Miss Wyntha Tompkins, Middlesex Health Association, Essex, Mass., Secretary.

NEW MEXICO MEDICAL SOCIETY, Roswell Senior High School, Roswell, May 2-4. Mr. Ralph R. Marshall, 221 West Central Ave., Albuquerque, Secretary.

NEW YORK, MEDICAL SOCIETY OF THE STATE OF, Hotel Statler, New York, May 7-11. Dr. Walter P. Anderton, 386 Fourth Ave., New York 16, Secretary.

NORTH CAROLINA, MEDICAL SOCIETY OF THE STATE OF, Hotel Carolina, Pinehurst, April 30-May 2. Dr. Millard D. Hill, 203 Capitol Bldg., Raleigh, Secretary.

OHIO STATE MEDICAL ASSOCIATION, Cleveland, Apr. 10-13. Mr. Charles S. Nelson, 79 East State St., Columbus 15, Executive Secretary.

OHIO STATE RADIOLOGICAL SOCIETY, Deshler-Hilton Hotel, Columbus, May 11-13. Dr. John R. Hannan, 10515 Carnegie Ave., Cleveland 6, Secretary.

OKLAHOMA STATE MEDICAL ASSOCIATION, Municipal Auditorium, Oklahoma City, May 6-9. Mr. R. H. Graham, 1227 Classen Drive, Oklahoma City, Executive Secretary.

REGIONAL MEETINGS:

AMERICAN COLLEGE OF GASTROENTEROLOGY:

New Orleans, Auditorium, Louisiana State University, April 8. Mr. Daniel Weiss, 33 West 60th St., New York 23, Executive Secretary.

AMERICAN COLLEGE OF PHYSICIANS:

Southern Illinois, Springfield, March 24. Dr. Charles H. Drenckhahn, 602 West University Ave., Urbana, Governor.

AMERICAN COLLEGE OF SURGEONS:

Edmonton, Alberta, Canada, The Macdonald, Apr. 23-25. Dr. J. Rose Vant, 10113, 104th St., Edmonton, Alberta, Canada, Chairman.

U. S. SECTION, INTERNATIONAL COLLEGE OF SURGEONS:

San Jose, Calif., St. Claire Hotel, March 22-23. Dr. Charles Mathe, 450 Sutter St., San Francisco 8, Chairman.

Madison, Wis., Loraine Hotel, April 26-28. Dr. Arnold S. Jackson, Jackson Clinic, Madison, Wis., Chairman.

Chattanooga, Tenn., Read House, April 30-May 1. Dr. William G. Stephenson, 546 McCallie Ave., Chattanooga 3, Tenn., Chairman.

RHODE ISLAND MEDICAL SOCIETY, Rhode Island Medical Society Library, Providence, May 1-3. Dr. Thomas Perry Jr., 106 Francis St., Providence 3, Secretary.

SOCIETY OF BIOLOGICAL PSYCHIATRY, Morrison Hotel, Chicago, Apr. 28-29. Dr. George N. Thompson, 2010 Wilshire Blvd., Los Angeles 5, Secretary.

SOCIETY OF NEUROLOGICAL SURGEONS, Memphis, Tenn., May 7-8. Dr. Bronson S. Ray, 525 East 68th St., New York 21, Secretary.

SOCIETY FOR PEDIATRIC RESEARCH, The Inn, Buck Hill Falls, Pa., May 6-11. Dr. Sydney S. Gellis, 330 Brookline Ave., Boston 15, Secretary.

SOUTHEASTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION, Hollywood, Fla., Mar. 25-29. Dr. Robert F. Sharp, 200 Carondelet St., New Orleans 12, Secretary.

SOUTHERN NEUROSURGICAL SOCIETY, George Washington Hotel, Jacksonville, Fla., Mar. 23-24. Dr. William F. Meacham, Vanderbilt University Hospital, Nashville 5, Tenn., Secretary.

SOUTHERN OREGON MEDICAL SOCIETY, Klamath Falls, May 9. Dr. Calvin Hunt, 1842 Esplanade St., Klamath Falls, Secretary.

SOUTHWESTERN SURGICAL CONGRESS, Pioneer Hotel, Tucson, Ariz., Apr. 16-18. Dr. C. M. O'Leary, 207 Plaza Court Bldg., Oklahoma City, Secretary.

STUDENT AMERICAN MEDICAL ASSOCIATION, Hotel Sherman, Chicago, May 4-6. Mr. Russell F. Staudacher, 510 North Dearborn St., Chicago 10, Executive Secretary.

SYMPOSIUM ON FUNDAMENTAL CANCER RESEARCH, Texas Medical Center, Houston, Texas, Mar. 29-31. Dr. Grant Taylor, University of Texas, Postgraduate School of Medicine, Houston, Texas, General Chairman.

SYMPOSIUM ON PEDIATRICS, Salt Lake City, Apr. 12-13. Dr. F. Willis Taylor, 1265 West 4th North, Salt Lake City 16, Chairman.

TENNESSEE STATE MEDICAL ASSOCIATION, Peabody Hotel, Memphis, Apr. 8-11. Dr. R. H. Kampmeier, 112 Louise Ave., Nashville 5, Secretary.

TEXAS MEDICAL ASSOCIATION, Galveston, Apr. 21-25. Mr. C. Lincoln Williston, 1801 N. Lamar Blvd., Austin, Executive Secretary.

THE CONSTANTINIAN SOCIETY, Del Monte Lodge, Pebble Beach, Calif., Apr. 11-14. Dr. C. F. Shook, P. O. Box 1035-36, Toledo 1, Ohio, Secretary.

UNITED STATES-MEXICO BORDER PUBLIC HEALTH ASSOCIATION, Mexicali, Baja Calif., and Calexico, Calif., Apr. 13-16. Dr. Sidney B. Clark, 204 U. S. Court House, El Paso, Texas, Secretary.

WESTERN INDUSTRIAL MEDICAL ASSOCIATION, Hotel Ambassador, Los Angeles, Apr. 28. Dr. Edward J. Zaik, 740 S. Olive St., Room 220, Los Angeles 14, Secretary.

WESTERN SECTION, AMERICAN UROLOGICAL ASSOCIATION, Sheraton-Palace Hotel, San Francisco, April 30-May 3. Dr. James Ownby Jr., 516 Sutter St., San Francisco, Chairman.

WISCONSIN, STATE MEDICAL SOCIETY OF, Hotel Schroeder, Milwaukee, May 1-3. Mr. Charles H. Crownhart, 330 East Lakeside St., Madison 1, Secretary.

FOREIGN AND INTERNATIONAL

ASSOCIATION OF INDUSTRIAL MEDICAL OFFICERS, London School of Hygiene and Tropical Medicine, London W.C.1, England, Sept. 24-28, 1956. Dr. J. A. A. Mekelburg, Peek, Frean and Company, Ltd., Keetons Rd., Bermondsey, London, S.E.16, England, Honorable Secretary.

BRITISH MEDICAL ASSOCIATION, Brighton, England, July 9-13, 1956. Dr. Angus Macrae, B. M. A. House, Tavistock Square, London, W.C.1, England.

CANADIAN MEDICAL ASSOCIATION, Québec, P. Q., Canada, June 10-14, 1956. Dr. Arthur D. Kelly, 150 St. George St., Toronto 5, Ont., Canada, Secretary.

CONFERENCE OF INTERNATIONAL UNION FOR HEALTH EDUCATION OF THE PUBLIC, Rome, Italy, April 27-May 5, 1956. Mr. Lucien Viborel, 92 rue St. Denis, Paris 1er, France, Secretary-General.

CONGRESS OF FRENCH SOCIETY OF OPHTHALMOLOGY, Paris, France, May 6-10, 1956. Dr. Marcel Kalt, 81 rue Saint-Lazare, Paris 9e, France, Secretary.

CONGRESS OF INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, Miami Beach, Fla., U.S.A., April 9-12, 1956. For information write: Mrs. L. McMechan, 318 Hotel West Lake, Rocky River, Ohio, U. S. A.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LIMNOLOGY, Helsinki, Finland, July 26-Aug. 7, 1956. For information address: Dr. H. Luther, Snellmansgatan 16 C 36, Helsinki, Finland.

CONGRESS OF INTERNATIONAL ASSOCIATION OF LOGOPEDICS AND PHONIATRICS, Barcelona, Spain, Sept. 3-7, 1956. Dr. J. Perello, Provenza 319, Barcelona 9, Spain, Secretary-General.

CONGRESS OF INTERNATIONAL SOCIETY OF HEMATOLOGY, Hotel Somerset, Boston, Mass., U.S.A., Aug. 27-Sept. 1, 1956. Dr. W. C. Moloney, 39 Bay State Road, Boston, Mass., U.S.A., Secretary.

CONGRESS OF INTERNATIONAL UNION AGAINST TUBERCULOSIS, New Delhi, India, Jan. 3-6, 1957. For information address: Secretariat, The Union, 66 Boulevard Saint-Michel, Paris 6e, France.

CONGRESS OF LATIN SOCIETY OF OPHTHALMOLOGY, Madrid, Spain, April 24-28, 1956. For information address: Dr. Costi, Montalban 3, Madrid, Spain.

EUROPEAN CONGRESS OF ALLERGOLOGY, Florence, Italy, Sept. 12-15, 1956. Prof. Umberto Serafini, Instituto de Patologia Medica, Viale Morgagni, Florence, Italy, Secretary-General.

EUROPEAN CONGRESS OF CARDIOLOGY, Stockholm, Sweden, Sept. 10-14, 1956. Dr. Karl Erik Grewin, Sodersjukhuset, Stockholm, Sweden, General Secretary.

EUROPEAN SYMPOSIUM ON VITAMIN B_{12}, Hamburg, Germany, May 22-26, 1956. For information write: Doz. Dr. H. Bauer, Nervenklinik, Hamburg-Eppendorf, Germany.

HEALTH CONGRESS, ROYAL SOCIETY FOR THE PROMOTION OF HEALTH, Blackpool, England, April 24-27, 1956. Mr. P. Arthur Wells, 90 Buckingham Palace Road, London S.W. 1, England, Secretary.

INTER-AMERICAN CONGRESS OF CARDIOLOGY, Havana, Cuba, Nov. 4-10, 1956. For information address: Dr. Ramon Aixala, Apartado 2108, Havana, Cuba.

INTERNATIONAL ACADEMY OF PATHOLOGY, Cincinnati, Ohio, U. S. A., April 24-25, 1956. Dr. F. K. Mostofi, Armed Forces Institute of Pathology, Washington 25, D. C., U. S. A., Secretary.

INTERNATIONAL CONGRESS AGAINST ALCOHOLISM, Istanbul, Turkey, Sept. 10-15, 1956. For information address: International contre l'Alcoolisme, Case Gare 49, Lausanne, Switzerland.

INTERNATIONAL CONGRESS ON ANIMAL REPRODUCTION, Arts School, University of Cambridge, Cambridge, England, June 25-30, 1956. Dr. Joseph Edwards, Production Division, Milk Marketing Board, Thames Ditton, Surrey, England, Hon. Secretary.

INTERNATIONAL CONGRESS OF ANTHROPOLOGICAL AND ETHNOLOGICAL SCIENCES, Philadelphia, Pa., U. S. A., Sept. 2-9, 1956. Dr. William N. Fenton, National Research Council, Division of Anthropology and Psychology, 2101 Constitution Avenue, Washington 25, D. C., U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF DIETETICS, Congress Palace, Esposizione Universale Roma, Rome, Italy, Sept. 10-14, 1956. Prof. E. Serianni, Associazione Dietetica, Italiana, via dei Penitenzieri N. 13, Rome, Italy, Secretary General.

INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Cologne, Germany, Aug. 19-23, 1956. Mr. Murray Kornfeld, 112 East Chestnut St., Chicago 11, Illinois, U. S. A., Executive Director.

INTERNATIONAL CONGRESS OF ENTOMOLOGY, Montreal, Canada, Aug. 17-25, 1956. Mr. J. A. Downes, Science Service Bldg., Carling Ave., Ottawa, Ont., Canada, Secretary.

INTERNATIONAL CONGRESS OF GASTROENTEROLOGY, London, England, July 18-21, 1956. Mr. Hermon Taylor, London Hospital, White Chapel, London E.1, England, Honorable Secretary.

INTERNATIONAL CONGRESS OF HEALTH TECHNICIANS, Maison de la Mutualite, Paris, France, June 5-8, 1956. For information address: Mr. M. H. Thoillier, 37 Rue de Monthion, Paris 9e, France.

INTERNATIONAL CONGRESS FOR THE HISTORY OF SCIENCE, Florence and Milan, Italy, Sept. 3-10, 1956. Dr. M. L. Bonelli, Instituto di Ottica, Arcetri, Florence, Italy, Secretary-General.

INTERNATIONAL CONGRESS OF HUMAN GENETICS, Copenhagen, Denmark, Aug. 1-6, 1956. For information address: The University Institute for Human Genetics, Tagensvej 14, Copenhagen N, Denmark.

INTERNATIONAL CONGRESS OF HYDATID DISEASE, Athens, Greece, Sept. 14-18, 1956. Prof. B. Kourias, Croix-Rouge Hellenique, 1 rue Mackenzie King, Athens, Greece, Secretary-General

INTERNATIONAL CONGRESS ON INFECTIOUS PATHOLOGY, Lyon, France, May 24-26, 1956. General Secretariat: Institut Pasteur de Lyon, 77 rue Pasteur, Lyon, France.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE, Madrid, Spain, Sept. 19-23, 1956. Dr. J. C. De Oya and Dr. J. Gimena, Hostaleza No. 90, Madrid, Spain, Secretaries.

INTERNATIONAL CONGRESS OF INTERNATIONAL COLLEGE OF SURGEONS, Palmer House, Chicago, Illinois, U. S. A., Sept. 9-13, 1956. Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Illinois, U. S. A., Secretary-General.

INTERNATIONAL CONGRESS OF MEDICAL RADIOPHOTOGRAPHY, Paris, France, April 4-7, 1956. For information address: Secretariat, 66 Boulevard Saint Michel, Paris 6e, France.

INTERNATIONAL CONGRESS ON MEDICAL RECORDS, Shoreham Hotel, Washington, D. C., U. S. A., Oct. 1-5, 1956. For information address: Miss Doris Gleason, Executive Director, American Association of Medical Record Librarians, 510 North Dearborn St., Chicago 10, Illinois, U. S. A.

INTERNATIONAL CONGRESS OF NEO-HIPPOCRATIC MEDICINE, Montecatini, Terme, Italy, May 20-22, 1956. Dr. Valente, 41 Avenue Verdi, Montecatini Terme, Italy, Secretary-General.

INTERNATIONAL CONGRESS OF PAEDIATRICS, Copenhagen, Denmark, July 22-27, 1956. Professor P. Plum, Rigshospitalet, Copenhagen, Denmark, President.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Copenhagen, Denmark, August 20-24, 1956. Dr. B. Strandberg, Kobenhavns amts sygehus I Gentofte, Dept. of Rheumatology and Physical Medicine, Hellerup, Denmark, Honorable Secretary.

INTERNATIONAL CONGRESS OF RADIOLOGY, Mexico, D. F., Mexico, July 22-28, 1956. Dr. Jose Noriega, Tepic 126 (2e piso), Mexico, D. F. 7, Mexico, Secretary General.

INTERNATIONAL CONGRESS OF WORLD CONFEDERATION FOR PHYSICAL THERAPY, Hotel Statler, New York, New York, U. S. A., June 17-23, 1956. For information address: Miss Mildred Elson, American Physical Therapy Association, 1790 Broadway, New York 19, New York, U. S. A.

INTERNATIONAL GENETICS SYMPOSIUM, Tokyo and Kyoto, Japan, Sept. 6-12, 1956. For information address: Secretary, International Genetics Symposium, Science Council of Japan, Ueno Park, Tokyo, Japan.

INTERNATIONAL PHYSIOLOGICAL CONGRESS, Brussels, Belgium, July 29-Aug. 5, 1956. For information address: Prof. J. Reuse, Faculte de Medicine et de Pharmacie, 115 Boulevard de Waterloo, Brussels, Belgium.

INTERNATIONAL PROFESSIONAL UNION OF GYNECOLOGISTS AND OBSTETRICIANS, Madrid, Spain, Sept. 28-29, 1956. Dr. Jacques Courtois, 1 rue Racine, St-Germain-en-Laye (S and O), France, Permanent International Secretary-General.

INTERNATIONAL SYMPOSIUM ON DIENCEFALON, Musec della Scienza e della Tecnica, Piazza S. Vittorre 21, Milan, Italy, May 3-5, 1956. Drs. S. Curri and L. Martini, Instituto di Farmacologia, Universita di Milano, via Andre del Sarto 21, Milan, Italy, Secretaries.

INTERNATIONAL SYMPOSIUM ON VENEREAL DISEASES AND THE TREPONEMATOSES, Hotel Statler, Washington, D. C., U. S. A., May 28-June 1, 1956. For information address: Dr. Charles A. Smith, Chief, Venereal Disease Program, Division of Special Health Services, Public Health Service, Dept. of Health, Education and Welfare, Washington 25, D. C., U. S. A.

LATIN AMERICAN CHAPTER, INTERNATIONAL SOCIETY OF ANGIOLOGY, Havana, Cuba, Nov. 8-11, 1956. Dr. Armando Nuñez Nuñez, 25 No. 510 Vedado, Havana, Cuba, President.

MEDICAL WOMEN'S INTERNATIONAL ASSOCIATION, EXTRAORDINARY GENERAL ASSEMBLY, Burgenstock, Nidwalden, Switzerland, Sept. 21-24, 1956. Dr. Janet Aitken, 30a Acacia Road, London N.W. 1, England, Secretary.

MIDDLE EAST MEDICAL ASSEMBLY, Campus, American University of Beirut, Beirut, Lebanon, April 7-9, 1956. Dr. Virgil C. Scott, American University of Beirut, Beirut, Lebanon, Chairman.

NATIONAL CONGRESS OF PEDIATRICS, Cuidad Universitaria, Mexico D.F., Mexico, May 1-5, 1956. Dr. Ignacio Avila Cisneros, Calzada de Madereros No. 240, Mexico 18, D.F., Mexico, Coordinator.

NORTH QUEENSLAND MEDICAL CONFERENCE, Cairns, North Queensland, Australia, June 25-30, 1956. Dr. W. R. Horsfall, P. O Box 672, Cairns, N.Q., Australia, Secretary.

PAKISTAN MEDICAL CONFERENCE, University of Peshawar, Peshawar, Pakistan, Apr. 2-4, 1956. Dr. M. W. Alivi, 9, Braganza House, Napier St., Saddar, Karachi, Pakistan, Secretary General.

PAN AMERICAN CONGRESS ON CANCER CYTOLOGY, Miami, Fla., U. S. A., April 2-6, 1957. Dr. J. Ernest Ayre, 1155 N.W. 14th St., Miami, Fla. U. S. A., General Chairman.

PAN AMERICAN CONGRESS OF GERONTOLOGY, Mexico, D. F., Mexico, Sept. 5-15, 1956. Dr. Manuel Payno, Avenue Cuahtemoc No. 10-3, Mexico 7, D. F., Mexico, Presidente.

PAN AMERICAN CONGRESS OF OTORHINOLARYNGOLOGY AND BRONCHOESOPHAGOLOGY, San Juan, Puerto Rico, April 8-12, 1956. Dr. C. E. Munoz MacCormick, Apartado 9111, Santurce 29, Puerto Rico, Secretary General.

PAN AMERICAN TUBERCULOSIS CONGRESS, Medellin and Bogota, Columbia, South America, Aug. 1-15, 1956. General Secretary, 26 de Marzo 1065, Montevideo, Uruguay.

WORLD CONGRESS ON FERTILITY AND STERILITY, Naples, Italy, May 18-24, 1956. Dr. Maxwell Roland, 114-20 Queens Boulevard, Forest Hills 75, New York, N. Y., U. S. A., Chairman, Liaison Committee.

WORLD FEDERATION FOR MENTAL HEALTH, Munich, Germany, Aug. 12-18, 1956. Secretariat, 19 Manchester Street, London W.1, England.

WORLD MEDICAL ASSOCIATION, Havana, Cuba, Oct. 9-15, 1956. Dr. Louis H. Bauer, 345 East 46th St., New York 17, New York, U. S. A., Secretary-General.

EXAMINATIONS AND LICENSURE

EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY: *Written.* Various locations in the United States and Canada, July 20. Final date for filing application was Jan. 20. *Oral.* Miami Beach, Mar. 18-22. Sec., Dr. C. B. Hickcox, 80 Seymour St., Hartford 15, Conn.

AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY. *Written.* Various centers, July 26. *Oral.* St. Louis, Oct. 12-15. Final date for filing applications is April 1. Sec., Dr. B. M. Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 15, 1956. Final date for filing application is May 1. *Oral Examinations in 1956.* Los Angeles, April 12-14; Chicago, June 7-9. Final date for filing application for these three oral examinations was Jan. 3. New York City, Sept. 21-25. Final date for filing application is April 1. *Cardiovascular Disease.* Chicago, June 6. The number of candidates is limited to 24 and the final date for filing applications is Apr. 2. Exec. Sec., Dr. William A. Werrell, 1 West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: St. Louis, May 3-5. Sec., Dr. Leonard T. Furlow, 660 South Kingshighway, St. Louis.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: *Oral and Pathological Examinations. Part II.* Chicago, May 11-20, 1956. Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Practical Examination.* San Francisco, June 18-21, St. Louis, Oct. 20-24. *Written.* Jan. 21, 1957. Applications must be filed before July 1, 1956. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland 9, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part I. Oral and written.* Various centers, April, 1956. Final date for filing application was Nov. 30. *Oral. Part II.* Chicago, January 1957. Final date for filing application is Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Ave., Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY. *Oral.* Montreal, Canada, May 6-10. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: *Pathologic Anatomy and Clinical Pathology.* Boston, April 18-20. Final date for filing application is March 15. Sec., Dr. Edward B. Smith, 1040 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral, Part II.* Atlanta, March 2-4. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION. *Parts I and II.* Chicago, June 16-17. Sec., Dr. Earl C. Elkins, 200 First St., S. W., Rochester, Minn.

AMERICAN BOARD OF PLASTIC SURGERY. *Entire Examination.* Buffalo, May 13-15. Final date for filing case reports was Jan. 1. Corres. Sec., Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Oral and Written. Public Health.* Given at Columbia, California, Harvard, Tulane and Minnesota schools of public health. *Aviation Medicine.* Chicago, April 13-15. Sec., Dr. Ernest L. Stebbins, 615 N. Wolfe St., Baltimore.

AMERICAN BOARD OF PROCTOLOGY: *Part I.* Philadelphia, May 5. Final date for filing application was March 15. Sec., Dr. Stuart T. Ross, 520 Franklin Ave., Garden City, N. Y.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: Philadelphia, April 16-18, 1956. Sec., Dr. David A. Boyd, 102-110 Second Ave. S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: Atlanta, Ga., Mar. 6-10. Final date for filing application was Dec. 1.; Chicago, June 5-9. Final date for filing applications was Jan. 1.; Los Angeles, Sept. 30-Oct. 4. Final date for filing applications is June 1. Sec., Dr. B. R. Kirklin, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Part I.* Centers throughout the United States, in Europe and in the Far East, March 28. Closing date for the March examination was December 1. *Part II.* Durham, March 12-13; Boston, May 14-15 and Philadelphia, June 4-5. Sec., Dr. John B. Flick, 255 S. Fifteenth St., Philadelphia.

AMERICAN BOARD OF UROLOGY: February 1957. Sec., Dr. William Niles Wishard, 1711 N. Capitol Ave., Indianapolis 7.

BOARD OF THORACIC SURGERY. *Written.* Various centers throughout the country, September. Final date for filing application is July 1. Sec., Dr. William M. Tuttle, 1151 Taylor Ave., Detroit 2.

MAGAZINE–TELEVISION REPORT

The following list of current medical articles in mass-circulation magazines and forthcoming network television programs on medical subjects is published each week only for the information of readers of THE JOURNAL. *Unless specifically stated, the American Medical Association neither approves nor disapproves of the articles and programs reported.*

TELEVISION

Monday, March 26

NBC-TV, 11 a. m. - noon, EST. "Medical and Health News with Howard Whitman."

MAGAZINES

Cosmopolitan, March, 1956

"Skin Deep," by Donald G. Cooley

A comprehensive article on skin and skin problems.

Parade, March 18, 1956

"What's Happened to the Sulfa Drugs," by Robert P. Goldman

Although the antibiotics now receive more publicity, the author says sulfonamides are still widely used for four reasons: "First some people develop sensitivity to penicillin and other antibiotics. Second, sulfas apparently can knock out certain infections just as well as or better than antibiotics. Third, sulfas gradually have been made safer. Finally, they are cheaper to produce—and use—than some antibiotics."

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GOVERNMENT SERVICES

AIR FORCE

Inspection Tour of Aviation School.—Assistant Secretary of Defense Dr. Frank B. Berry, in private life professor of clinical surgery at Columbia University, New York, arrived at Randolph Air Force Base in Texas Feb. 8 for a two-day inspection tour of the School of Aviation Medicine. With Dr. Berry was Major Gen. Dan C. Ogle, surgeon general of the Air Force, and more than a dozen physicians who serve as advisors to the Defense Department.

In the party were Drs. Stanhope Bayne-Jones, director of research in the Army Surgeon General's Office, and Howard Karsner, research advisor to the Navy's Bureau of Medicine and Surgery; Melvin A. Casberg, Dr. Berry's predecessor in the defense post; Thomas P. Fox, D.D.S., Philadelphia; Oscar P. Hampton, St. Louis; Anthony J. J. Rourke, professor of hospital administration, Leland Stanford University; James L. Tullis of Harvard Medical School; Dwight L. Wilbur, professor of clinical medicine at Stanford; Harwood S. Belding, University of Pittsburgh; Truman G. Blocker, University of Texas; Donald W. Hastings, University of Minnesota; Maynard K. Hine, University of Indiana; Harold C. Hodge, University of Rochester; Richard A. Kern, Temple University; Christian Lambertsen, University of Pennsylvania; Carl V. Moore, Washington University, St. Louis; Waltman Walters, Mayo Clinic in Rochester, Minn.; James P. Hollers, D.D.S., San Antonio; Mrs. Mildred L. McBlair, executive secretary of the advisory council; and Lieut. Col. William C. Burry, secretary of the advisory panel.

The program consisted of a series of briefings on research and teaching at the school and a visit to the school's radiobiology laboratory in Austin, Texas.

ARMY

Symposium in Honolulu on Trauma.—A five-day symposium on acute trauma, sponsored by the Tripler Army Hospital department of surgery, will be held April 2-6, with the department's head, Col. George L. Beatty, as chairman. An attendance of 200 island doctors, civilian and military, is expected. Discussion will deal primarily with noncombat trauma, such as injuries received in training, traffic accidents, and household mishaps. Individual speakers will be allotted 40 minutes, with 10 minutes for questions and answers. Subject matter will emphasize case histories.

Brig. Gen. John F. Bohlender, hospital commandant, will open the assembly, 8 a. m., April 2. Program subjects are Body Reaction to Injury; Injuries of the Head, Central Nervous System; Thoracic Injuries; Abdominal Injuries; Skeletal Trunk, Urinary Tract Injuries; Thermal, Traumatic Soft Tissue Injuries; Skeletal Injuries, Upper and Lower Extremities.

PUBLIC HEALTH SERVICE

Research on Hospital and Health Services.—Grants totaling $230,833 for research to develop new knowledge relating to hospital and health services and facilities were announced Feb. 10 by the surgeon general. The awards, which will be made to two hospitals, two health organizations, and a university, are the second group of Public Health Service grants designed to aid research in the hospital facilities field. Congress appropriated $1,200,000, under the Hospital Survey and Construction Act, for grants to qualified nongovernmental research scientists, on recommendation of the federal hospital council. Eleven grants totaling $401,960 were approved in December. Additional applications will be considered at the council's March meeting.

The five research projects are as follows:

Sinai Hospital, Baltimore: a demonstration to find the extent to which the shortage of professional nurses can be alleviated by employing and training floor managers and general aides for nonprofessional duties in a hospital nursing unit, $35,190.

St. Mary's Hospital, Evansville, Ind.: evaluation of a new plan undertaken by the hospital to provide more individual care for patients, together with a demonstration of the reorganization and education necessary to the success of such a plan, $31,843.

The Health Insurance Plan of Greater New York: an analysis of statistical information to determine the influence of a comprehensive medical care insurance program on hospital admissions, patients' length of stay, quality of service given, and hospital costs, $30,000.

American Hospital Association: a basic analysis of what the nation has accomplished in the past decade in planning and building hospitals and health facilities, including evaluation of the effect of the Hill-Burton and other construction programs, for the purpose of establishing new scientific guides to planning for the hospitals, nursing homes, rehabilitation centers, and diagnostic and treatment centers that will be needed in the future, $109,650. The project is designed to furnish modern yardsticks for deciding how many hospital beds and what services will be needed, how hospital costs should be determined, and similar questions.

Yale University, New Haven, Conn.: a study to determine operation factors that can be used as guides in the planning of hospital architectural design to achieve maximum functional efficiency, $24,150.

Members of New Allergy Council.—Appointment of 10 members to the newly established National Advisory Allergy and Infectious Diseases Council has been announced by the surgeon general. The council was set up to facilitate activities of the new National Institute of Allergy and Infectious Diseases, one of seven National Institutes of Health that comprise the principal research branch of the Public Health Service. On recommendation of the council, the surgeon general will award grants to scientists in universities and other nonfederal institutions for research on allergy and infectious diseases. The council held its first meeting March 7-8 at the National Institutes of Health, Bethesda, Md. At present two vacancies remain on the council.

The members are: Dr. René J. Dubos, Rockefeller Institute for Medical Research, New York; Dr. Karl F. Meyer, University of California Medical Center, San Francisco; Dr. Gail M. Dack, Food Research Institute, University of Chicago; Dr. Edwin B. Fred, president, University of Wisconsin, Madison; Dr. Charles E. Smith, dean, School of Public Health, University of California, Berkeley; Dr. H. O. Halvorson, head, department of bacteriology, University of Illinois; Mr. Byron H. Larabee, president, Firestone Plantations Company, Akron, Ohio; Mr. David C. Crockett, associate director, Massachusetts General Hospital, Boston; Mrs. Rollin Brown of Los Angeles, president, National Congress of Parents and Teachers; Mr. John Abbink of New York, president, American Foundation for Tropical Medicine.

Joseph A. LePrince Dies.—Joseph Augustin LePrince, a pioneer in sanitary engineering, who died in Memphis, Tenn., Feb. 10, served as a commissioned officer of the Public Health Service from 1914 until he retired in 1939. Previously he achieved distinction as the right-hand man of Major Gen. William Gorgas in the control of yellow fever, malaria, and other diseases in the Panama Canal Zone while the canal was under construction. He was public health officer of the zone from 1904 to 1914. A native of Leeds, England, Mr. LePrince came to the United States in 1887. In 1898 he was graduated from Columbia University, where he received degrees in civil engineering. Mr. LePrince was co-author of "Mosquito Control in Panama," which became known as the "Bible of mosquito control."

Poliomyelitis Vaccine.—The Public Health Service announced Feb. 14 that a total of 34,154,274 cc. of poliomyelitis vaccine had been released since April, 1955. The states and territories have received 19,870,308 cc. of poliomyelitis vaccine; the National Foundation for Infantile Paralysis 13,721,226 cc.; and 562,740 cc. went into commercial channels before voluntary controls were established.

DEATHS

Walker, Arthur Meeker ✠ Washington, D. C.; born in Pittsfield, Mass., Sept. 26, 1896; Harvard Medical School, Boston, 1923; interned at the Massachusetts General Hospital in Boston; from 1938 to 1941 associate professor of pharmacology at the University of Pennsylvania School of Medicine in Philadelphia, where he joined the faculty in 1925 as an instructor in pharmacology and in 1929 became assistant professor; certified by the National Board of Medical Examiners; member of the American Physiological Society, College of Physicians of Philadelphia, Society for Pharmacology and Experimental Therapeutics, American Society for Clinical Investigation, American Trudeau Society, and the National Tuberculosis Association; on the advisory council of the Leonard Wood Leprosy Foundation; served overseas during World War I and was decorated with Purple Heart with Palm; served during World War II; in 1941-1942 was assistant to chairman and from September, 1945, to January, 1946, historian, committee on medical research, Office of Scientific Research and Development; from 1946 to 1950 director, chemotherapy, tuberculosis service, Veterans Administration, and since 1950 chief, research and education, tuberculosis service, Veterans Administration; editor of Veterans Administration Technical Bulletins, Series 10; died Dec. 12, aged 59.

Harris, Richard Lamar ✠ Montrose, N. Y.; born in Wrightswood, Ga., Oct. 25, 1897; University of Georgia Medical Department, Augusta, 1920; assistant professor of clinical psychiatry at Cornell University Medical College in New York City; formerly on the faculty of his alma mater; specialist certified by the American Board of Psychiatry and Neurology; member of the Association of Military Surgeons of the United States; fellow of the American Psychiatric Association and the American College of Physicians; served during World War II; member of the advisory board of the Association for Physical and Mental Rehabilitation; began his career in the Veterans Administration in 1921, serving as chief of the neurological service at the Diagnostic Center in Washington, D. C., manager of the Veterans Administration Hospital at Sheridan, Wyo., and chief medical officer at the Brentwood division of the Veterans Administration Hospital in Los Angeles; manager of the Veterans Administration Hospital in Montrose, where he died Nov. 22, aged 58, of coronary thrombosis.

Shanklin, Eldridge Madison ✠ Hammond, Ind.; born in Carroll County, Ind., Oct. 31, 1875; Medical College of Indiana, Indianapolis, 1902; member of the House of Delegates of the American Medical Association, 1927-1928, and in 1947 resigned as a member of the advisory board of the Cooperative Medical Advertising Bureau; one of the founders, for 25 years secretary, and in 1920 president of the Lake County Medical Society; in 1925 president of the Indiana State Medical Association; for 10 years councilor of the Tenth District, which he served as chairman; for many years a member of the state board of medical registration and examination, of which he had been vice-president, president, and secretary; one of the founders of the Indiana Academy of Ophthalmology and Otolaryngology; editor of the *Journal of the Indiana State Medical Association* from 1933 to 1948, when he became editor emeritus; served on the staff of St. Margaret's Hospital, where he died Jan. 5, aged 80, of uremia and arteriolar nephrosclerosis.

Allen, John Calvin, Henderson, Texas; Tulane University of Louisiana School of Medicine, New Orleans, 1923; served during World War II; died Nov. 22, aged 57, of acute anterior coronary occlusion.

Farres, Shickry, Canton, Ohio; Bennett Medical College, Chicago, 1912; died Dec. 12, aged 75.

Haley, Clarence Foster ✠ Brooksville, Ky.; University of Louisville School of Medicine, 1919; secretary of the Bracken County Medical Society; on the courtesy staff of Hayswood Hospital in Maysville; died Oct. 10, aged 68, of acute coronary thrombosis.

✠ Indicates Member of the American Medical Association.

Haley, William Thomas ✠ Marblehead, Mass.; Tufts College Medical School, Boston, 1913; specialist certified by the American Board of Otolaryngology; fellow of the American College of Surgeons; served on the faculty of his alma mater; on the staffs of the Boston City and St. Elizabeth's hospitals in Boston; died in Gainesville, Fla., Jan. 22, aged 73, of anterior myocardial infarction.

Hannah, Walter White ✠ Mountain Home, Tenn.; University of Tennessee College of Medicine, Memphis, 1947; interned at the Baltimore City Hospitals, where he served a residency; resigned from the U. S. Army on Jan. 21, 1954; affiliated with the Veterans Administration; died Dec. 23, aged 32.

Hegge, Rolv Sigvard, Austin, Minn.; University of Minnesota Medical School, Minneapolis, 1929; past-president of the Mower County Medical Society; an associate member of the American Medical Association; served as health officer of Mower County; on the staff of St. Olaf Hospital, where he died Dec. 3, aged 53, of cerebral hemorrhage.

Herndon, Lewis Sidney ✠ East Orange, N. J.; Medical College of Virginia, Richmond, 1914; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons; served on the staffs of the City Hospital and St. Michael's Hospital in Newark and St. Mary's Hospital in Orange, where he died Dec. 31, aged 66, of tumor on the lung.

Howard, Willard Samuel ✠ St. Paul, Minn.; University of Illinois College of Medicine, Chicago, 1914; associated with the Veterans Administration; died Dec. 17, aged 66, of coronary thrombosis.

Howell, Henry Amasa, Holdenville, Okla.; Atlanta College of Physicians and Surgeons, 1901; served during World War I; on the staff of St. Francis Hospital; died in the Veterans Administration Hospital in Sulphur Nov. 26, aged 81, of myocardial degeneration.

Hughes, Reese William, Pittsburgh; Maryland Medical College, Baltimore, 1906; died Oct. 28, aged 81, of cerebral thrombosis.

Jones, Le Roy, Albuquerque, N. Mex.; Lincoln (Neb.) Medical College of Cotner University, 1910; veteran of the Spanish-American War and World War I; formerly associated with the Indian Service; died Dec. 4, aged 79, of coronary occlusion.

Kamerer, Samuel Alden, West Sunbury, Pa.; Western Pennsylvania Medical College, Pittsburgh, 1901; served during World War I; died in the Butler County Memorial Hospital in Butler Nov. 28, aged 83, of bronchopneumonia.

Kirkpatrick, Alva M., Lake Wales, Fla.; Medical College of Ohio, Cincinnati, 1889; died Oct. 31, aged 91, of coronary occlusion.

Latimer, Newton J. ✠ Corning, Ark.; Kentucky School of Medicine, Louisville, 1895; University of Louisville (Ky.) Medical Department, 1896; also a registered pharmacist; in 1954 honored at "Dr. Latimer Day" by the Young Men's Civic Club for his many years of untiring and unselfish service to those who were in need; died Dec. 29, aged 86.

Lebenstein, Joseph, New York City; University and Bellevue Hospital Medical College, New York City, 1899; affiliated with the city board of health; consultant, Hospital for Joint Diseases; died Dec. 18, aged 78, of cerebral hemorrhage.

Lincoln, Cicero Lee ✠ Denver; Washington University School of Medicine, St. Louis, 1909; member of the American Trudeau Society; for many years president of the Denver Tuberculosis Society; served as medical director of the Swedish National Sanatorium in Englewood; on the staffs of St. Luke's and Mercy hospitals; died Jan. 7, aged 69, of coronary occlusion.

Lunn, Edwin De Moss, Bay City, Texas; University of Texas School of Medicine, Galveston, 1924; specialist certified by the American Board of Otolaryngology; died Nov. 30, aged 57.

UNIVERSITY OF MICHIGAN LIBRARIES

McDowell, William Patton ✠ Norfolk, Va.; Medical College of Alabama, Mobile, 1900; specialist certified by the American Board of Pediatrics; charter member of the American Academy of Pediatrics; past-president of the Norfolk County Medical Society and the Virginia Pediatrics Society; on the consulting staff, pediatric service of Norfolk General, De Paul, and Leigh Memorial hospitals; died Dec. 30, aged 79, of a heart attack.

Mantia, Mario Francis, Darien, Ga.; Hahnemann Medical College and Hospital of Philadelphia, 1937; died Dec. 21, aged 55.

Miller, Austin Vicente ✠ Porterville, Calif.; Cooper Medical College, San Francisco, 1899; chief of staff at the Tulare County Hospital in Tulare from 1935 to 1950; died in the Stanford University Hospital, San Francisco, Dec. 31, aged 78, of cerebral hemorrhage.

Miller, Hilma Catherine Louise Swanson, Los Angeles; Eclectic Medical University, Kansas City, Mo., 1915; died Dec. 25, aged 72.

Minahan, John James ✠ Chilton, Wis.; Marquette University School of Medicine, Milwaukee, 1915; served during World War I; formerly member of the school board and county coroner; on the staff of St. Agnes Hospital in Fond du Lac, where he died Dec. 14, aged 67, of dissecting abdominal aortic aneurysm.

Morrison, Harry Kavanaugh, Leesburg, Fla.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1902; died Dec. 9, aged 79.

Nemens, Harry S. ✠ New York City; Long Island College Hospital, Brooklyn, 1926; fellow of the American Academy of General Practice; on the staffs of the Beth David Hospital and Riverside Hospital; died in the Doctors Hospital Jan. 9, aged 54, of coronary thrombosis.

Nexsen, Harold, Brooklyn, N. Y.; Long Island College Hospital, Brooklyn, 1910; served on the staffs of the Long Island College and Brooklyn hospitals; died Dec. 7, aged 69, of coronary occlusion.

Nofer, George Hancock, Philadelphia; Jefferson Medical College of Philadelphia, 1902; an associate member of the American Medical Association; on the staffs of the Episcopal Hospital and St. Mary's Hospital, where he died Jan. 12, aged 76, of injuries received when struck by an automobile.

Patterson, Willard Albert, Brunswick, Ga.; Meharry Medical College, Nashville, Tenn., 1915; died Nov. 20, aged 65, of pyelonephritis and hypertensive cardiovascular disease.

Phillips, James Benajah, Jr. ✠ Chattanooga, Tenn.; Vanderbilt University School of Medicine, Nashville, 1939; interned at the Vanderbilt University Hospital in Nashville and the James M. Jackson Hospital in Miami, Fla.; president-elect of the Chattanooga and Hamilton County Medical Society; served overseas during World War II; on the staffs of the Erlanger Hospital and Memorial Hospital, where he died Jan. 6, aged 41, of a heart attack.

Phipps, Howard Morton, Hempstead, N. Y.; Columbia University College of Physicians and Surgeons, New York City, 1911; member of the Medical Society of the State of New York; past-president of the Nassau County Medical Society; served as coroner's physician for Nassau County; physician for the Hempstead public school system; on the staff of the Meadowbrook Hospital; died Jan. 16, aged 69, of carcinoma of the lungs.

Scodel, Bension, Butlerville, Ind.; Tufts College Medical School, Boston, 1921; formerly affiliated with the Fort Wayne (Ind.) State School; on the staff of the Muscatatuck State School, where he died Oct. 21, aged 65, of coronary occlusion.

Simon, Emil Robert ✠ Detroit; Wayne University College of Medicine, 1938; specialist certified by the American Board of Urology; fellow of the American College of Surgeons; on the staffs of the Grace, Sinai, and Brent hospitals in Detroit, and Wayne County General Hospital in Eloise; died Dec. 23, aged 43, of aortic stenosis.

Skaggs, D. Randolph, Ashland, Ky.; Hospital College of Medicine, Louisville, 1907; died Nov. 3, aged 84, of bronchopneumonia and uremia.

Smedley, Charles William, Cleves, Ohio; Cincinnati College of Medicine and Surgery, 1897; died Oct. 27, aged 94, of bronchopneumonia and generalized arteriosclerosis.

Smith, Edward Michael, Washington, D. C.; Jefferson Medical College of Philadelphia, 1912; served during World War I; formerly physician at the New York Athletic Club in New York City; died Nov. 11, aged 75, of coronary infarction.

Smith, George Herbert, Baltimore; University of Maryland School of Medicine and College of Physicians and Surgeons, Baltimore, 1952; veteran of World War II; served a rotating internship at the University Hospital, after which he spent two years as assistant resident in psychiatry; since July 1, 1955, U. S. Public Health Service fellow in psychiatry at his alma mater; died suddenly Nov. 7, aged 34, of coronary thrombosis.

Sommerfield, William Ansel ✠ Sarasota, Fla.; Western Reserve University School of Medicine, Cleveland, 1931; member of the Arizona State Medical Association; served during World War II; died in Bradenton Nov. 26, aged 48.

Stammer, Emanuel Louis, Plainview, N. Y.; Long Island College Hospital, Brooklyn, 1919; died Nov. 21, aged 60, of glioblastoma.

Stein, Robert, Senior Assistant Surgeon, U. S. Public Health Service, reserve, Portland, Maine; Indiana University School of Medicine, Indianapolis, 1953; began active duty in the U. S. Public Health Service Reserve in 1953; died Nov. 21, aged 26.

Stough, William Vesta ✠ Montgomery, Ala.; University of Alabama School of Medicine, Mobile, 1907; died in Gulf Shores Nov. 24, aged 75, of coronary occlusion and hypertension.

Tesar, Frank Joseph ✠ Centreville, Mich.; University of Illinois College of Medicine, Chicago, 1936; interned at St. Luke's Hospital in Chicago, where he was formerly a resident at the Research and Educational Hospital; served during World War II; on the staff of the Three Rivers (Mich.) Hospital; died Jan. 14, aged 44, of gastrointestinal hemorrhage and cirrhosis of the liver.

Tompkins, Charles Ernest ✠ Benton Harbor, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1900; died in the Mercy Hospital Nov. 6, aged 80, of cerebral thrombosis and arteriosclerosis.

Truitt, Crawford Sylvanous, Daingerfield, Texas; Barnes Medical College, St. Louis, 1908; member of the State Medical Association of Texas; past-president of the Morris County Medical Society; city health officer; at one time mayor; surgeon for the Louisiana, Arkansas, and Texas Railroad; served as president of the Chamber of Commerce; died in a Gilmer (Texas) hospital Oct. 29, aged 77, of cardiac asthma.

Wallace, Harry M., Greenville, Va.; University College of Medicine, Richmond, 1901; died in Staunton Oct. 30, aged 82, of arteriosclerotic heart disease.

Wallach, Isidor Arthur ✠ Los Angeles; Ohio State University College of Medicine, Columbus, 1928; member of the American Academy of General Practice; on the staff of the Hollywood Presbyterian Hospital; died Jan. 28, aged 53.

Walters, Arthur Edward, St. Louis; St. Louis University School of Medicine, 1907; died in St. Mary's Hospital Nov. 3, aged 82, of cerebral vascular hemorrhage, cerebral arteriosclerosis, generalized arteriosclerosis, and arteriosclerotic heart disease.

Webb, Frederick Leon, Clinton, S. C.; Emory University School of Medicine, Atlanta, 1914; member of the South Carolina Medical Association; medical director of the Whitten Village Infirmary; died Jan. 10, aged 63, of coronary thrombosis.

White, Charles Alexander, Cazenovia, N. Y.; Medical College of Virginia, Richmond, 1900; died Oct. 28, aged 78, of cerebral vascular accident and hypertension.

Wills, Thomas Opie ✠ Corsicana, Texas; University of Texas School of Medicine, Galveston, 1918; on the staffs of the Corsicana and Navarro Clinic hospitals; died Jan. 14, aged 59, of coronary occlusion.

Witt, Carl Brent ✠ Louisville, Ky.; Hospital College of Medicine, Louisville, 1904; died Jan. 9, aged 77, of a heart attack.

FOREIGN LETTERS

BRAZIL

Survival in Inoperable Breast Cancer.—The need for a determination of a mean survival time in patients with inoperable breast cancer, to serve as a standard of comparison with the survival in patients operated on, led Dr. Alfredo Abrão and his co-workers to analyze a series of 106 such patients (*Rev. paulista med.* **47**:417, 1955).The series included 45 patients who had never had any surgical treatment, 30 who had been operated on and were admitted with inoperable relapses, and 31 in whom bilateral oophorectomy had been performed. Of the first group, 13 were dropped from the study because their case histories were unavailable. Of the remaining 32 patients, 3 were still alive at 39, 35, and 30 months after the onset of the illness and 29 had died. The mean survival time of those who had died was 41.1 months after the onset of their illness and 13.2 months after the first visit to the cancer clinic. The shortest survival time was three months and the longest 10 years. There was no case of spontaneous regression, the course being always steadily progressive. The ages of the patients at the first visit varied from 28 to 86 years (average 51.1). Of the 32 patients not operated on, 17 received no treatment at all and 15 were given testosterone propionate in weekly dosages of 150 to 700 mg. for four-month periods, with one to three-month intervals. For three of the patients on whom radical mastectomy had been performed, no case history was available. Of the remaining 27 patients who had relapses after operation, 2 were still alive 100 and 123 months after the onset of the disease and 91 and 65 months, respectively, after the operation. These two had metastases when they first came to the cancer clinic 40 and 36 months after operation. The mean survival time for the 25 patients who died was 61 months after the onset of the disease, 46.6 months after operation, and 11.2 months after the first visit to the cancer clinic. The shortest survival after operation was one month and the longest five years. Of the patients subjected to oophorectomy, 26 had died. Their ages varied from 30 to 76 years (average 50.4), and their mean survival time was 25.7 months after the onset of the illness. The shortest survival time was 3 months and the longest 101 months. Since the performance of oophorectomy, the mean survival time of the patients who died was 4.7 months, the shortest time being one month and the longest 22 months. The mean survival time for patients who were subjected to mastectomy and then to oophorectomy was 6 months after the castration and 2.9 months for those in whom mastectomy was not previously performed.

Birth Trauma.—Neme and Araujo in *Revista de gynecologia e d'obstetricia* (**49**:281, 1955) reported their review of the different types of birth trauma observed at the Hospital das Clinicas from Jan. 1, 1944, to Dec. 31, 1952, which was undertaken to ascertain whether the medical care offered at that hospital had reduced or aggravated the incidence of those lesions. Their series included 7,885 deliveries (7,373 nonsurgical and 512 by forceps) of babies weighing over 1,500 gm. (3.5 lb.). Those weighing less were excluded, as most of them were born without obstetric interference. In this series intracranial hemorrhage occurred in 14 (0.18%), a low incidence, even in comparison with recent statistics of the most advanced medical centers. According to the authors, this low rate was due largely to skill and care in delivering breech presentations. High forceps were almost never used. Of the five cases of cerebral hemorrhage associated with the 512 interventions, forceps were used in four. Brachial paralysis occurred in 17 (0.21%) of the deliveries and lesions of the facial nerve in 39 (25 cases of paralysis and 14 of paresis), a rate of 0.49%. All but two of the injuries to the facial nerve were caused by the application of forceps. In the entire series there were 19 fractures, or a rate of 0.24%; 17 of these were fractures of the collarbone. This injury frequently goes undetected, accounting for the lower incidence reported by some other observers. One fracture of the humerus and one of the occiput were reported. Cephalhematoma occurred in 11 cases, a rate of 0.14%; all of these occurred with use of forceps.

The items in these letters are contributed by regular correspondents in the various foreign countries.

FRANCE

Colonic Contractions.—Justin-Besançon and his co-workers (*Semaine hôp. Paris* **32**:5, 1956) introduced a sound with a small air bag into the sigmoid flexure in a proctoscopic examination. A constant air pressure in the bag was maintained, and a pneumatic device made it possible to record the colonic contractions on a slowly rotating cylinder. By studying the tracings it was easy to differentiate not only the normal and constipated subjects but also subjects with the atonic type of constipation in which the tracings showed practically complete absence of contractions and subjects with the spasmodic type in which the contractions are shown to be more extended and frequent than normal.

J. Guerre studied the effect of potassium on colonic motility by the same (sigmoidographic) method (*Semaine hôp. Paris* **32**:12, 1956). Potassium was given either by mouth in the dose of 1 gm. per kilogram of body weight or intravenously in the dose of 10 mEq. dissolved in 200 cc. of dextrose and serum in the course of recording the tracing. Hypoglycemia and hypokalemia were induced and tests done with other patients, and some subjects were given 1.5 gm. of potassium chloride daily and subjected to a recording after a course of this treatment. An analysis of the results shows that, in subjects with either a normal or a spastic colon, the potassium has no effect but that it restores the impaired colonic motility in subjects with atonic constipation.

Detection of Tuberculosis in Children.—Douady and his coworkers (*Semaine hôp. Paris* **32**:145, 1956) state that, if a case of active tuberculosis occurs in a school child, tuberculin tests of all the children in the same classroom are performed. Statistics on a large scale, such as those of the 4 million tests given in 1953, are hard to interpret because of errors due to faulty technique, the number of subjects who are not tested due to parental opposition or absence, or the number who are absent on the day the test is read. Such statistics, however, show a notable drop in the rate of positive tests in the last 50 years. They have also indicated some local variations due to the density of the population and the social structure of the community. Study of the results of the tuberculin tests, which were done with sufficient regularity in two departments, has allowed a better assessment of tuberculization in school children. Since the percentage of positive findings, as compared with the number of tests carried out, does not give a sufficiently precise index, an index that takes into account the number of children showing a change in reaction was used. This index sets up a ratio between the number of changes in reaction occurring in the interval (usually one year) between two series of tuberculin tests and the number of negative tests in the later series. It is especially informative for assessing the need for a mass x-ray campaign. A rising index would indicate such a need.

INDIA

Liver Abscess.—A. P. Bhattacharya in the *Indian Medical Forum* (**6**:349 [Nov.] 1955) reported the case of a 22-year-old man who was admitted to hospital because of irregular fever, pain in the right upper abdominal quadrant, gradual emaciation, enlargement of the abdomen, difficulty in breathing, and swelling of the ankles of two to four weeks' duration. There was a history of trauma in the right hypochondrium. He had been vomiting for three days prior to admission. His pulse rate was 140 per minute and his blood pressure was 90/60 mm. Hg. The abdomen was rigid, tender, tympanitic, and silent on auscultation.

The right side of his chest was dull on percussion and the breath sounds were diminished. Aspiration of the liver yielded chocolate-colored fluid containing degenerated liver cells. Culture of this material yielded no organisms. The patient was given antibiotics and observed. As his general condition improved, liver aspiration was repeated and 200 cc. of chocolate-colored fluid was removed. Aspiration was repeated again after two days, as the patient was having severe respiratory embarrassment. On the fifth day the abdominal distension was relieved by puncturing the peritoneal cavity in the right iliac fossa, and 500 cc. of chocolate-colored fluid containing degenerated liver cells was removed. After this the patient was markedly improved. Abdominal aspiration was repeated every two or three days, and he was given emetine. Within two months the edema disappeared, the patient gained weight, and he had no trouble except for occasional pain in the abdomen and chest and tenderness over the liver. Liver aspiration was therefore repeated, and another course of emetine was given. At the time of discharge, after about three months, the patient was free of symptoms and his general condition was improved.

Tropical Eosinophilia.—Ganatra and Lewis in the *Indian Journal of Medical Sciences* (**9**:672 [Nov.] 1955) stated that, although arsenicals have been found effective in patients with tropical eosinophilia, the mode of action of arsenic is little understood. Preparations for oral use are supposed to be less effective than those for parenteral use. The clinical and radiological improvement is, however, not always accompanied by a return of the formed elements of the blood to normal. This is usually delayed and may take two to four months. Various other drugs have recently been tried. In the present study, 13 consecutive patients, who were on an ambulatory regimen, were treated with diethylcarbamazine and the results compared with those of a control group of 13 consecutive patients treated with carbarsone. All had the classical triad of symptoms: cough, attacks of difficulty in breathing, and general debility. The total leukocyte count and the total eosinophil count were estimated in all of them. No patient was included in this study unless the total eosinophil count was above 5,000 cells per cubic millimeter. One tablet of carbarsone (0.26 gm.) was given twice daily for 10 days. The dose of diethylcarbamazine was 13 mg. per kilogram of body weight for four days. The results with use of this drug compared well with those obtained with carbarsone. The fall in total eosinophil counts was quicker with diethylcarbamazine, but an early temporary exacerbation of symptoms was noted more frequently than with use of carbarsone.

Treatment of Leprosy.—Dharmendra and Sen in *Leprosy in India* (**27**:180 [July] 1955) reported that trophic ulcers are a troublesome and often intractable complication of leprosy. They are most commonly seen on the undersurface of the foot. For the purpose of dressing these ulcers, the authors used a by-product of 4,4′-diaminodiphenylsulfone present in the filtrate after the final extraction of 4,4′-diaminodiphenylsulfone by a certain process. This viscous fluid contained 2,4-diaminodiphenylsulfone, some 4-nitro-4′-aminodiphenylsulfone, and traces of 4,4′-diaminodiphenylsulfone, iron, and 4′, 4-diaminodiphenylsulfoxide. In some of the patients so treated the trophic ulcers were improved. A regular study was therefore started on 22 patients, most of whom had tuberculoid lesions. All of these patients were also getting 4,4′-diaminodiphenylsulfone by mouth. The local treatment with the new product proved to be more satisfactory than treatment with some other substances commonly used. Complete and permanent healing cannot, however, be expected with any local application, if diseased and dead bone lies at the bottom of the ulcer. For permanent healing, the diseased bone has to be removed. Steps must also be taken to improve the circulation of the part, and it must be protected against constant pressure and repeated injuries.

Chemical Changes at Site of Allergic Manifestation.—Chatterji and Banerji in the *Bulletin of the Calcutta School of Tropical Medicine* (**3**:160 [Oct.] 1955) stated that urticarious lesions have been attributed to the liberation of acetylcholine or histamine at the site of the lesions, due perhaps to an associated defect in the production of cholinesterase or histaminase. The authors extracted a portion of skin from the site of the lesion in hydrochloric acid solution. An extract of skin from the quiescent site of a previous urticarious lesion was also tested for comparison. Both extracts showed the presence of histamine, but the former contained 3.5 times more than the latter. A preliminary experiment with the normal skin from a dermographic subject, as well as from a site of active dermographia, did not reveal any histaminic activity.

Sciatica in Brucellosis.—T. N. Mathur in the *Indian Journal of Medical Sciences* (**9**:698 [Nov.] 1955) noted that brucellosis is not often considered in the etiology of sciatica and is often treated symptomatically, though sciatica may be a symptom or complication of brucellosis. Brachial neuritis occurring as a complication of this condition has also been described. The author reported three cases of brucellosis. In one of the three patients sciatica developed during the acute febrile stage, and in the other two it occurred six months after the febrile stage. One of them showed lipping of the bodies of the vertebrae. Brucella melitensis was isolated from two patients. It is important to keep this condition in mind while diagnosing sciatica and to rule it out before any treatment is given.

Free Treatment to Tuberculous Patients.—The Delhi state authorities are considering a scheme to provide free treatment to all tuberculous patients having less than a specified income. There are about 20,000 such patients in Delhi. Additions to the bed strength of hospitals and clinics are being made, and by the end of the current fiscal year there will be about 1,000 beds for tuberculous patients in Delhi.

ISRAEL

Medical Research.—A. de Vries in a lecture at the third World Assembly of the Israel Medical Association stated that, because of the climate, because of the primitive conditions and habits of a part of the population, and because of the importation of diseases by immigrants, many infectious diseases are prevalent in Israel. This fact stimulated research in the field of viral, parasitic, and bacterial disease. An important contribution in this field was the work on West Nile fever. The virus of this disease, known previously in Africa, was isolated in Israel from a sick child during an epidemic of an acute infectious disease in a communal settlement. Thus, for the first time, the virus was related to a characteristic clinical entity with fever, rash, headache, abdominal pain, vomiting, pain in the back and limbs, swollen lymph nodes, and neurological disturbances. It was found that the virus is antigenically related to that of type B (Japanese) epidemic encephalitis and that of type C (St. Louis) epidemic encephalitis. Another contribution was the development of a living rabies virus vaccine by serial passage through eggs. The virus became avirulent but remained antigenic. It is used to immunize dogs and is accepted for that purpose by the World Health Organization. In the future it may prove of value in immunizing human beings. Much work is also being done on poliomyelitis. It was found that about 50% of the population of Jerusalem and of the recent immigrants from Yemen had, by the time they reached the age of 2 or 3 years, developed antibodies against poliomyelitis virus, type 2 (Lansing), as demonstrated by the mouse neutralization test. At present, poliomyelitis virus, type 1, 2, and 3, is being isolated from patients by using the tissue culture method. The poliomyelitis virus has also been found responsible for some cases of encephalitis. In addition, Coxsackie virus was isolated from many patients with poliomyelitis and also from a few with aseptic meningitis.

A rare parasite, possibly Haemogregarina, was discovered in the leukocytes of the peripheral blood in a patient with a prolonged febrile disorder accompanied by hepatosplenomegaly and albuminuria. Other experiments are concerned with the resistance of Trichomonas vaginalis to chemical reagents. It was found that Trichomonas resistant to stilbamidine isethionate absorbs the drug into the cytoplasm but does not react to it. The nature of the resistance of these organisms to colchicine was found to be twofold: resistance against the lethal action and resistance against the inhibition of division of the protoplasm during mitosis. These types of resistance are distinct and independent from each other. Serologic studies of Leishmania have shown that visceral leishmaniasis is antigenically different

in different parts of the world. Also, the Donovan bodies are antigenically different from Leishmania donovani in the flagellate stage. While cases of jaundice due to leptospiral infection have probably occurred in Israel for many years, Leptospira grippotyphosa was only recently isolated from such patients. The source of infection was probably the field mouse. Other animals found to be infected with different types of Leptospira are the goat, pig, dog, sheep, and mule. While Lept. grippotyphosa causes severe liver changes, the liver was not found to be damaged in Lept. canicola infection.

Spermine and spermidine from human semen have been found inhibitory to the growth of Micrococcus pyogenes var. aureus, Shigella, and other bacteria. Basic synthetic polyamino acids such as polylysine have also been found to have a bacteriostatic action. Streptomycin-dependent strains of Brucella abortus injected into mice do not cause brucellosis in the mouse but do produce immunity to it. Also, the streptomycin-dependent strain caused antibody formation without causing disease. It has also become possible to immunize mice, rabbits, and guinea pigs with streptomycin-dependent Vibrio comma without causing cholera. These strains are also being used for bioassay of streptomycin in human body fluids and secretions.

Hematologists have shown that human thrombocytes may be classified into the blood groups O, A, B, and AB, corresponding to those of the red blood cells, and that the natural isoagglutinins for the red blood cells are also isoagglutinins for the thrombocytes. The arrival of so many new immigrants provided a unique opportunity to study the blood group distribution among the different ethnic groups. It was found that among the Jews from Yemen, Persia, and Kurdistan the Rh-negative blood group was less frequent than in those of European or American birth. The highest frequency of Rh-negative blood was found in those from Cochin and Tripoli. It has been observed here that apparently healthy groups living in an adequate social environment have a hemoglobin level that is lower than that of similar groups in other so-called civilized countries. More serious is the anemia among pregnant women, especially of the recent immigrant group, which seems to be due in part to iron deficiency. The study of patients with hemorrhagic disease has contributed to the knowledge of selective disturbances in platelet function in thrombocytopathies. Fetal hemoglobin levels can now be determined as a measure of the extent of blood replacement in exchange transfusions for hemolytic disease of newborn infants. Studies of interactions between basic synthetic polypeptides, blood cells, and plasma enzymes indicate that these synthetic polymers agglutinate red blood cells. This has furnished a model for electron-microscopic studies of the forces acting in red blood cell agglutination. The basic polypeptides also retard the coagulation of whole blood by an antithromboplastic action, accelerate the clotting of fibrinogen, and retard fibrinolysis. They promote phagocytosis in vitro and increase capillary permeability. Electrophoretic studies of hemoglobin at varying ionic strengths and temperatures have led to the detection of four fractions in normal hemoglobin and to the finding of a hitherto undescribed abnormality of hemoglobin in patients with atypical congenital hemolytic anemia.

Cervical cancer was found to be rare in Jewish women as compared to women in most parts of the world. As no external causes such as nutrition or hygienic habits could be found responsible for the low frequency, a genetic factor is suspected. On the other hand, the frequency in mammary, ovarian, and noncervical uterine cancer varies in different Jewish communities, being more frequent in the European and American groups. The incidence of all carcinomas was 15% and was higher in patients of African, Asian, and Israeli origin.

On the basis of the concept that progesterone is the substance that causes menstrual bleeding, it has become possible to induce bleeding in the intermenstruum by giving progesterone when the endometrium is primed by estrogen. This led to treating amenorrhea with progesterone. By studying crystallization of the cervical mucus, it was shown that male hormones could be transformed into female hormones in women. Furthermore, as progesterone inhibits mucous crystallization, endometrial biopsy can be replaced in a high percentage of cases by the mucus test, demonstrating the formation of a corpus luteum. Although in the premenstruum it is possible to induce crystallization by estrogens, this is impossible during pregnancy, because there is no crystallization of mucus at this time, since the cervical cells lose their permeability to the electrolytes. A pregnancy test based on this finding has been devised.

SWITZERLAND

New Indications for Prednisone.—G. Bickel of Geneva gave prednisone to a few patients with pulmonary emphysema or fibrosis who had become invalids. In four patients, dyspnea on exertion was attenuated and capacity for movement was extended. Loss of weight was noted at the beginning of treatment, showing that there had been latent water retention. Vital capacity was significantly increased, both on effort and at rest, indicating a return to a better degree of pulmonary elasticity. A favorable effect of the drug was also noted in patients with refractory cardiac insufficiency. Two patients in the terminal stages of coronary disease, with irreducible asystole, were dramatically benefited by a treatment of less than 10 days' duration. Twenty-five to 30 gm. of prednisone was given daily and caused a weight reduction of 8 kg. (18 lb.) in one and 14 kg. (31 lb.) in the other. This result was accompanied by a return of sensitivity to mercurial diuretics. The diuresis occasioned by the corticosteroids in refractory cardiopathies never occurs immediately. It starts on the fifth or sixth day of treatment, then quickly reaches its maximal intensity. With the use of cortisone, water diuresis appears to be greater than that of sodium. The favorable action of cortisone on refractory asystole raises the question of the genesis of edema in congestive heart failure. Formerly it was attributed to increased venous pressure, but more recently it has been pronounced the result of faulty blood supply to the kidneys, with increased reabsorption of sodium by the tubules. The latter phenomenon is related to the increased production of mineralocorticoids, especially aldosterone, so often seen in cardiac patients. This in turn seems to be the result of hyperfunction of the anterior lobe of the pituitary. The diuresis caused by cortisone and prednisone could be explained by the stimulating action they exert on glomerular filtration and also by their partial antagonism to certain of the mineralocorticoids. Cortisone may have a direct effect on water metabolism and may neutralize the antidiuretic hormone of the hypophysis. Patients with congestive heart failure are known to have excessive amounts of that hormone.

Neurovegetative Dystonia.—P. A. Gloor (*Schweiz. med. Wchnschr.* **85**:1209, 1955) studied 100 men and 100 women with dystonic syndromes in an effort to distinguish somatic and psychic predisposing factors. Some of these patients are true neuropaths, that is, they have serious, permanent disorders of the neurovegetative system causing chronic subjective symptoms that persist from childhood and are often accompanied by allergic manifestations and low resistance to infectious diseases. On the other hand, there indubitably exist the classic dystonias described by internists as following trauma, intoxication, or infection. Some are of purely psychopathological origin. In the past, the psychic factors have been neglected in favor of the somatic factors. In more than 70% of Gloor's series of patients, psychic derangement appears to have conditioned the somatic manifestations, and only in 25% could the psychopathic disorders be said to be clearly secondary to the bodily disease. When dystonia becomes established, a psychosomatic vicious circle is set up, causing psychic disturbances of a different nature, clearly distinct from the basic disorder. In about half of his patients, the author encountered fixation on symptoms. The dystonic syndrome may be a prodrome of more serious disease of more precise location, i. e., "organ neurosis." These are organic illnesses, at present being investigated for underlying psychic factors. In some patients with toxic goiter, gastric ulceration, dysmenorrhea, and certain dermatoses, psychotherapy has been successful.

Serologic Test for Syphilis.—Dr. J. Delacretaz of Lausanne recently analyzed 357 cases of possible or probable nonspecific serologic reactions and concluded that: (1) the Treponema pallidum immobilization test (Nelson's test) does not help in the differential diagnosis of treponematoses; (2) the test shows negative results in animals without treponematosis that present

positive serologic reactions; (3) in most cases in which a diagnosis of false-positive reaction has been made on the basis of the clinical findings, the T. pallidum immobilization test will be negative; since there is at present no absolute criterion for the diagnosis of latent syphilis, Delacretaz considers it probable that in these cases a positive result in this test means concomitant latent syphilis; (4) in unaccountable serologic reactions, i. e., where there are no signs of syphilis or other diseases known to cause false-positive serologic reactions, the T. pallidum immobilization test appears to be the method of choice for differentiating syphilitic from nonspecific reactions.

Relapses After Exeresis for Pulmonary Tuberculosis.—Naef of Lausanne and A. Rodel of Montana reexamined 250 of the 400 patients in whom they had performed pulmonary resection for tuberculosis and found that 22 relapses had occurred. In the 155 patients with lobectomy, there were 13 relapses; in 42 with pneumonectomy, 2; and in 53 with segmentectomy, 7. This does not rule out segmentectomy as an operative procedure; the higher percentage of relapses was probably due to errors in selection. Of the factors operative in causing relapses, the moment at which intervention was performed does not seem to be one, whereas distention of the remaining parenchyma, with resultant reopening of cicatricial foci, definitely plays a part. Distention should be avoided by prophylactic postresectional thoracoplasty. The length of postoperative medical and rest therapy is perhaps the most important factor, since many relapses are caused by its having been interrupted too soon. Segmentectomy should be reserved for those cases in which the disease is clearly limited to one segment. Naef and Rodel have stopped performing atypical, cuneiform, and enucleating exereses, because these are not anatomically justifiable and because they leave pulmonary tissue crushed, badly irrigated, badly ventilated, and therefore vulnerable.

World Census of Physicians.—There are now 1,200,000 physicians in the world, and the 595 medical schools operating in 85 countries graduate annually between 50,000 and 60,000 new doctors, according to Dr. J. L. Troupin of the World Health Organization. This study shows a great inequality in distribution among the world's 2.5 billion people. Only 14 countries have a ratio of one physician to every thousand or fewer people. There are 22 others where there is only one physician for 20,000 or more inhabitants. Between these two extremes, the rest of the 124 countries and territories that make up today's world show great variations that are even more meaningful, since the number of physicians engaged in teaching, research, administration, and other duties not directly connected with the care of patients must be taken into account. As a general rule, rural areas have a shortage while cities may have an overabundance of doctors. The study also shows that, while 9 countries have one medical school for less than 1 million people, 13 have only one such school for 9 to 17 million people.

Tuberculosis in Europe.—The Luxembourg Study Group of the World Health Organization reports that, due to new drugs and modern thoracic surgery, the risk of dying of tuberculosis today is much less than it used to be. Denmark and the Netherlands have the lowest death rates for tuberculosis in Europe and in the world. In countries with a low prevalence of tuberculosis, mass examinations reveal too few cases to be economically justified. Instead, efforts should be directed at special groups, particularly those exposed to infection and those likely to infect others. The study group concluded that a patient should not be considered cured until he has successfully taken up an active life in society again. Fear of employing the discharged patient is one of the difficulties in rehabilitation. A good job is, however, a good way of preventing a relapse, and the discharged patient who remains under close medical observation is much less dangerous to his fellow men than the undiscovered case.

New Test for Hemochromatosis.—W. Soltermann of Bern found hemosiderin in epithelial cells of apocrine sweat glands of the axilla in 100% of a series of patients with hemochromatosis. Iron was present in 86% of the samples taken from cadavers of patients who had died of this disease. The epithelial cells of holocrine sweat glands may also contain iron. Iron can be shown to be present in the basal layer and in the dermis of both healthy persons and patients with hemochromatosis. The quantity of hemosiderin discovered does not permit confirmation of a diagnosis of hemochromatosis. Histologically examined sections indicate that iron is excreted along with sweat. Turnbull's method is superior to the Prussian blue reaction in the performance of such a test. The presence of iron in the skin must be interpreted with care, even when it is not in the axilla. It is less important than the presence of the classic clinical symptoms of the disease.

Autodeviation of the Complement.—Prof. W. Jadassohn of the University of Geneva reported that in six and a half years 104,071 Bordet-Wassermann tests were made in the dermatology clinic. In 334 of these the reaction could not be determined because of autodeviation of the complement. He believes that age (over 50 years) is a factor in this phenomenon, but not sex. The influence of syphilis is certain. Of persons who presented one or more autodeviations, 40% were syphilitic, while of the whole group only 5% were syphilitic. Autodeviation of the complement is particularly frequent in newborn babies (cord blood). The number of autodeviations in adults is only three per thousand. There are significant differences in the number of autodeviations occurring in different years, which are probably explained by differences in the antisheep serums used.

Incidence of Tabes and General Paresis.—Twenty-five years ago Jadassohn's father wondered whether early energetic treatment of syphilis would increase the chances of late manifestations of the disease. A modern survey shows that in Geneva (population 200,000) 69 cases of tabes and general paresis were diagnosed in the last seven years. More than half of these date from the first two years of this period. The nervous forms of the disease seem, therefore, to be on the wane. The disease was checked much more effectively in persons infected during the period 1932 to 1937 than in those who contracted the disease in the period 1916 to 1918. Not only has the number of fresh cases decreased but the prognosis also has been improved. It is not known whether this change is spontaneous or due to better treatment.

Cytostatic Pomades.—E. Fischer of Zurich treated 30 patients with basal cell carcinoma or precancerous lesions of the skin locally over a period of 6 to 28 days with two salves, one containing 0.05% of colchicine and the other 0.1% of Demecolcin. Treatment was continued until the appearance of an erosive reaction. Half the patients were treated with 5% podophyllin in petroleum jelly or this preparation alternated with colchicine salve. In the entire group about 50% were cured, as judged by a follow-up lasting for one to three years. Thus, cytostatic therapy with pomades is not of value in every case, probably because the local action of the cytostatic agents is not deep enough.

Deaf-Mutism.—J. P. de Reynier of Lausanne reported to a group of otolaryngologists that in the five French-speaking cantons of Switzerland (population 1,051,400) there are about 733 deaf-mutes. Since 1894, when the first count was made, the number has been diminishing (in 1894, 245; in 1930, 170; now about 70 deaf-mutes per 100,000 inhabitants). This decrease is due to goiter prevention with iodized salt. At present, congenital dumbness predominates in Switzerland as in other countries. In patients with the acquired form, 11.9% had cranial trauma and 27% meningitis. While sulfonamides and antibiotics have decreased the mortality from meningitis, deafness from this disease has increased.

Vitamin E in Dermatoses.—I. Dainow of Geneva believes that the urticarias and eczemas of women that recur at a certain phase of the menstrual cycle are allergic reactions connected with some endocrine disturbance. He claims that by administering vitamin E one can curb the endocrine component of the process and achieve suppression of the cutaneous manifestations within three or four months.

New Treatment of Onychomycosis.—J. Walch of Zurich obtained encouraging results in the treatment of onychomycosis with a new fungicide, bortrioxybenzoic acid ester in a solvent containing alcohol and ethyl acetate. The latter mixture is a lipid solvent and has a dehydrating action on the skin. Changes in the proportions of the solvent alter the penetration power for either the skin or the nails.

UNITED KINGDOM

Guillebaud Report.—Owing to the mounting costs of the National Health Service, a committee under the chairmanship of Mr. C. W. Guillebaud was appointed in May, 1953, by the Minister of Health to inquire into the cost and general structure of the National Health Service. The committee reports that expenditure on the health service is not excessive. There is no definite objective standard of adequacy in a health service. The government must decide each year what it is going to spend, bearing in mind what it must allocate to other social services, and provide the best possible service for the money. No major change is reported as needed in the general administrative structure of the service to make it more efficient or economical. No recommendations are made for producing new sources of income, e. g., by increasing drug charges to patients, or for reducing in any substantial degree the annual cost of the service. In fact, the committee suggests that in some quarters, particularly in hospital capital expenditure and mental health, an adequate service can be supplied only by raising the present level of expenditure. The committee states that charges of widespread extravagance in money or manpower cannot be substantiated.

Nominal charges for hospital treatment to lower the cost of the health service is not recommended because there would be administrative difficulties and it would not be humanitarian. The committee does not favor limiting the list of prescribable drugs, but physicians should be kept informed of the cost of drugs, and they should review their prescribing of expensive drugs and the quantities of all drugs prescribed. Both physician and public should be educated away from the prevalent "bottle of medicine" habit. Neither the removal of the 14-cent prescription charge to patients nor its increase would materially affect the cost of the health service, nor would a returnable cash deposit for medicine containers. Similarly the committee believes that dental charges and charges for eyeglasses to the public should remain, although they might be reduced later. Owing to the shortage of dentists, the service should not be expanded and the employment of dental auxiliaries should be considered. The committee does not favor making a charge for ambulance service. Costs should be borne by the local health departments and not the hospitals, as at present.

The committee criticizes the present system of allocating hospital funds for the current fiscal year only. There is no long-term policy. The adoption of block grants to meet current expenditure in the hospital service is not favored nor is the carrying forward of unspent balances from one year to another. The amount of hospital capital investment is considered to be totally inadequate and cannot be allowed to remain the same much longer without serious harm. An annual figure of 54 million dollars is considered to be a desirable rate of capital expenditure for the hospital service for the next seven fiscal years. Hospital cost accounting needs to be improved so that certain standards of efficiency can be set and expenditure can be reviewed at the end of the year in relation to these standards. All hospitals should have a system of accounts that would make their budgetary control effective. At the beginning of the fiscal year, all hospitals should prepare a budget for the next 12 months and should endeavor to keep to it. The committee believes that residential accommodation and nursing should be provided for the aged who cannot be cared for in their own homes, although they may not need hospital treatment. This would increase local taxes, which local authorities are loath to do. A grant from the treasury might overcome the difficulty of financing such a scheme.

Amebiasis.—At a discussion on amebiasis by the Royal Society of Tropical Medicine and Hygiene in January, speakers emphasized the fact that diagnosis of the disease is important in Great Britain because the infection is often found in people who have never been abroad. Dr. A. Adams (Liverpool School of Tropical Medicine) said that a three-week course of emetine and bismuth iodide therapy was still the best treatment for acute intestinal amebiasis, with acetarsone as the next best drug. In his view the antibiotics had not justified themselves for routine use and should be used only for special cases. Prof. A. W. Woodruff (London School of Hygiene and Tropical Medicine) agreed that emetine and bismuth iodide was the drug of choice for the chronic intestinal form of the disease, with emetine itself for the acute attack. The relapse rate in his patients was only 3%. The effects of newer drugs did not compare with those of emetine. Sir Philip Manson-Bahr (London) agreed. The Liverpool team had tested the antibiotics chloramphenicol, chlortetracycline, oxytetracycline, and fumagillin, all of which had proved disappointing. Moreover, the continued use of antibiotics is not without danger. Camoform is unsatisfactory, but Glaucarubin and Entamide show promise and are cheap. Most of these drugs are less toxic than emetine. Sir George McRobert pointed out the danger of relying on antibiotics in the treatment of amebic hepatitis, which yields to emetine and chloroquine. Accurate diagnosis should be made before treatment, because sometimes patients who do not have the disease are treated with toxic drugs. Emetine is still too expensive for the peasant class in the tropics to use.

British Medical Journal Criticizes Ministry of Health.—The *British Medical Journal* has criticized the way in which the Ministry of Health publicized its scheme to issue poliomyelitis vaccine to local authorities. The *Journal* said that family physicians and health officers learned about it first from the press or over the radio and that the official circular sent to local health authorities contained no scientific information. It was considered deplorable that the Ministry of Health did not give the facts of the matter to the medical press so that it could be reported, with informed comment, to the medical profession before it reached the newspapers and the public. The *Journal* complains of lack of scientific data in the information given out to local authorities. There is no information on the culture medium or on the presence of small amounts of penicillin or streptomycin. The ministry is thus treating health officers as not much more than mechanics. Bacteriologists want to know, but are not informed, in what respects the two British vaccines differ from the Salk vaccine. It is most important that general practitioners should know what the children under their care are receiving. Even though a sensitivity reaction to penicillin may be most unlikely, the general practitioner would be on his guard if he knew that his young patient had received some in the vaccine.

Epileptic Drivers.—It is generally considered by coroners and by the Royal Society for the Prevention of Accidents that epilepsy is rarely a cause of traffic accidents. This view is not shared by Dr. Raymond Hierons (*Brit. M. J.* **1**:266, 1956), who discovered a number of accidents involving epileptic drivers. Three of these were locomotive engineers, one of them having been an engineer for 30 years. One was involved in an accident, and the other two in near accidents. Several others of these epileptics were truck drivers. One ran his truck into a stationary bus during an attack. Hierons observed 28 epileptics, all of whom had been involved in automobile or cycle accidents. In his opinion, however, coronary thrombosis is almost as frequent a cause of accidents as epilepsy and alcoholism is an even greater cause. Some well-controlled epileptics have been driving for years without accidents. Hierons reports the case of an epileptic taxi driver who has visited a hospital since 1906 and has continued with his work without attacks or accidents. In Great Britain epileptics who drive automobiles or mechanically propelled vehicles are breaking the law. Hierons thinks that the risks are small if an epileptic has been free from attacks for five years. He does not, however, think that the physician should inform motor-licensing authorities of patients suffering from epilepsy.

Thyroxine-like Activity of Tribromothyronine.—The demonstration of high thyroxine-like activity in man of analogues of thyroxine not containing iodine must cause a reorientation of our fundamental views on thyroid physiology. Compston and Pitt-Rivers, having shown that 3:5:3′-tribromo-DL-thyronine is active in preventing goiter in rats induced by thiouracil, administered the compound to patients with myxedema (*Lancet* **1**:22, 1956. In a dose of 1 mg. daily it restored normal metabolism in this condition. The activity of 1 mg. of DL-tribromothyronine daily was about the same as that of 260 mg. of desiccated thyroid daily, or of 0.4 mg. of L-thyroxine, which is the quantity contained in 260 mg. of desiccated thyroid. As the D-isomer of DL-tribromothyronine is devoid of thyroxine-like activity, L-tribromothyronine has only slightly less activity than thyroxine itself.

CORRESPONDENCE

UREMIA AND ECLAMPSIA

To the Editor:—The address of the Chairman of the Section on Obstetrics and Gynecology at the 1955 Annual Meeting of the American Medical Association (*J. A. M. A.* **160:**251-255 [Jan. 28] 1956) states that eclampsia "is still one of the three most common causes of maternal mortality" and that "uremia stands out as an almost exact counterpart." The author attributes the symptoms to toxins derived from protein metabolism and, therefore, states that the "logical approach would be to put the patient to bed to reduce protein breakdown from bodily activity, limit protein intake." This is an astonishing disregard of the universally established fact among students of the kidney that the outdated jumble of uremia has been separated into different components; most of the enumerated eclamptic symptoms (edema, retinal changes, high blood pressure, dizziness, and convulsions) have no relation whatever to azotemia or protein metabolism but are the recognized features of puerperal and nonpuerperal eclampsia, as defined by the French school and Volhard, and they strictly represent disturbances of salt and water metabolism. A few cases of puerperal intoxication of noneclamptic character, possibly connected with protein metabolism, are without edema, hypertension, or convulsions. I was the first American writer to propose a saltless diet for prophylaxis and treatment of eclampsia (Allen, F. M., and Sherrill, J. W.: *J. Metabolic Research* **2:**429-545 [Oct.] 1922; Allen, F. M.: Treatment of Kidney Diseases and High Blood Pressure, Morristown, N. J., The Physiatric Institute, 1925). This was first confirmed by Bernstein and Bland (*Am. J. M. Sc.* **173:**844-854 [June] 1927). For present status see Fishberg (Nephritis and Hypertension, ed. 5, Philadelphia, Lea & Febiger, 1954). If "the largest hospital in the world" still treats eclampsia by such mere symptomatic palliatives as bed rest and catharsis, some other hospitals also may need warnings against the discarded notion of "toxins." The known efficacy of abortion in preventing maternal mortality does not excuse unnecessary fetal mortality. If patients are placed on a correct low-sodium diet at the first premonitory symptoms, or at least before the terminal stage (with diuretics and other measures, if needed), both the incidence and the mortality of eclampsia can be reduced to the vanishing point. That is the conquest of eclampsia. The continuing death rate furnishes the amazing evidence that the lesson has not been learned in many quarters after these long years.

FREDERICK M. ALLEN, M.D.
1031 Fifth Ave.
New York 28.

RESERPINE AND THE NEWBORN INFANT

To the Editor:—I am fearful that an erroneous impression will be gathered from the data presented in Dr. Budnick's article (*A. M. A. Am. J. Dis. Child.* **90:**286 [Sept.] 1955) and particularly from an excerpt of the paper that appeared in THE JOURNAL (**160:**209 [Jan. 21] 1956). Parenterally given reserpine used alone or in combination with other hypotensive agents has been, since 1953, and is the principal method of managing toxemia and hypertension in pregnant patients at the District of Columbia General Hospital. To date, over 2,400 patients have been treated. The nasal congestion that Dr. Budnick mentions certainly is present in a fair incidence of babies. Attention was called to this in a previous report from this hospital (*Am. J. M. Sc.* **229:**379 [April] 1955). In this regard, it would seem that serious complications might be avoided by not allowing the infants so affected to assume the supine position, administering nasal vasoconstrictors, and duly orienting the nursery personnel. At this hospital it is believed that the use of reserpine is a simpler, more effective method of managing toxemia and hypertension of pregnancy. A definite impression has been gained that such therapy has improved infant and maternal mortality. To assess its true value, the charts of the 2,400 patients who have received reserpine and the babies delivered of these mothers are now being analyzed. A comparable group of records of toxemic and hypertensive mothers and babies treated with pentobarbital and magnesium sulfate are also being analyzed. Only then will the true value of reserpine be established and the true incidence of toxic reactions be realized.

FRANK A. FINNERTY JR., M.D.
The Georgetown University Medical Division
District of Columbia General Hospital
Washington 3, D. C.

EDWARD MARTIN LAVOR

To the Editor:—I am appealing for help in locating Edward Martin Lavor. Mr. Lavor is 40 years old, is about 5 ft. 9 in. (175 cm.) in height, and weighs about 150 lb. (68 kg.). He has dark brown eyes, dark brown hair, and a mole just above the corner of the right side of his mouth. He requires glasses for close work, as he is farsighted. He is a laboratory technician and has been on sick leave for the past several years. Mr. Lavor contracted pulmonary tuberculosis as the result of a laboratory accident. He has had a resection of the upper right lobe, followed by a thoracoplasty. There has been evidence of a reactivation of tuberculous foci in the lower right lobe and the upper and lower left lobes. This created a rather depressed state of mind. He went on a short trip to Los Angeles and was last heard from Dec. 15, 1955. Since then there has been absolutely no trace of him. It is believed that he undoubtedly will be in need of medical attention and work to support himself. If this man comes to anyone's attention, I would appreciate it if the person would call me collect (telephone, 6-8581).

Edward Martin Lavor.

LOUIS HIRSCH, M.D.
718 N. Country Club
Tucson 12, Ariz.

STRETCH SOCKS

To the Editor:—While examining a large number of young children for various foot and leg conditions, I have noticed an increasing tendency on the part of mothers to dress these children in stretch socks, some of which are rather snug fitting over the toes and cause quite a bit of bending and curving of the toes, particularly of the big and little ones. Knowing the effects of even relatively minor elastic pressure on the bending of bones, I wonder whether physicians should tend to advise against using this type of sock until some more definite investigative work has been done to show that there will be no ill-effects on the elastic-cartilaginous structures of children's small feet. I would like other physicians to consider this problem also. Possibly they will be stimulated to investigative action.

ALEX HARELL, M.D.
216 Wall Bldg.
Olive at Vandeventer
St. Louis 8.

MEDICAL LITERATURE ABSTRACTS

NEUROLOGY & PSYCHIATRY

Familial Occurrence of Multiple Sclerosis. B. Estborn. Nord. med. **54:**1665-1667 (Nov. 3) 1955 (In Swedish) [Stockholm, Sweden].

Genetic factors are believed to operate in the occurrence of multiple sclerosis. The author found reports of 33 families with three cases of multiple sclerosis each, 5 families with four cases each, and 1 family with five cases. He describes an additional family with five cases in two generations. In differential diagnosis, the possibility of spinocerebellar ataxia is especially to be considered. Spinocerebellar ataxia most often appears before the patient is 20 years old, the onset is insidious, and the course slowly progressive, while the onset of multiple sclerosis before the patient is 20 years old occurs in less than one-fifth of the cases and the initial symptoms are often violent, receding later or disappearing during the remissions typical of the course. The following criteria are set up for the diagnosis of multiple sclerosis: (1) onset between the ages of 12 and 50; (2) disseminated symptoms including symptoms from the pyramidal tract, heightened muscle reflexes, weakened or negative abdominal reflexes, positive Babinski reactions, disturbance of cerebellar functions (often with nystagmus), and disturbances in vision; (3) remissions and exacerbations; (4) generally increasing incapacity; (5) absence of clinical and serological signs of syphilis; and (6) changes in the colloid curve in the cerebrospinal fluid. Often not all the characteristics appear simultaneously.

The Action of Phenothiazine Derivatives in Multiple Sclerosis. H.-M. Seyffert. München. med. Wchnschr. **97:**1623-1625 (Dec. 2) 1955 (In German) [Munich, Germany].

Seyffert discusses the results that were obtained with derivatives of phenothiazine in 28 patients with multiple sclerosis. Fourteen of the patients had new attacks or acute exacerbations of multiple sclerosis. Thirteen of these 14 patients showed good remissions after from four to eight weeks of treatment. The improvement does not necessarily prove the value of the treatment, because spontaneous remissions are possible in this form of multiple sclerosis. Improvement was considerable in some of the patients with the chronic progressive form of multiple sclerosis. Response to the treatment was most evident in patients in whom spastic paralysis of the extremities dominated the clinical picture. In addition to the favorable influence on the symptoms of the pyramidal and extrapyramidal motor system, most patients also showed a more or less noticeable regression of the sensory impairment. Disturbances in the spinal sympathetic centers, such as bladder incontinence, also responded to this treatment. In patients who were subject to changes in moods and emotions the drugs had a stabilizing effect. The favorable effects were not so clear in patients in whom nystagmus, ataxia, and other disturbances in cerebellar coordination existed. In patients with these disorders, the phenothiazine derivatives could be combined with cocarboxylase. The treatment with the phenothiazine derivatives had to be continued for at least four to six weeks. Presumably these drugs normalize the sympathetic and the trophic processes in the diseased tissues and thereby increase the reparative capacity of the nervous system.

The place of publication of the periodicals appears in brackets preceding each abstract.

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Procaine Oil Blocking of the Globus Pallidus. H. Narabayashi, T. Okuma and S. Shikiba. A. M. A. Arch. Neurol. & Psychiat. **75:**36-48 (Jan.) 1956 [Chicago].

Paralysis agitans (Parkinson's disease) and postencephalitic Parkinsonism were considered at first to be different in etiology and neuropathology, but gradually it was realized that there were cases in which differentiation seemed impossible. The authors discuss the treatment of the rigidity and tremor of Parkinsonism by stereotactic injection of procaine hydrochloride in oil and wax. They believe that stereoencephalotomy, in addition to the opportunities for treatment, provides an approach to investigation of the function of the subcortical ganglia. Although it had been demonstrated by some that in postencephalitic Parkinsonism the substantia nigra was selectively affected, others produced evidence that the globus pallidus, corpus striatum, and thalamus were also involved. The authors survey surgical treatments that have been recommended for the hyperkinetic disorders and discuss the concept of blocking the globus pallidus. They performed stereotactically guided injections of the procaine oil and wax mixture into the globus pallidus for the treatment of Parkinsonism in 26 patients. The principal symptoms were dramatically influenced and relieved by this method, without any undesirable side-effects in most cases. Improvement was observed immediately after operation. Reduction of rigidity was sustained, but tremor showed a tendency to reappear within several weeks. Improvement in tremor depends on improvement of the coexistent rigidity. This operation is indicated mainly for rigidity and less for tremor. There was one fatality in the 26 operations. It was caused by intracerebral bleeding during insertion of the needle. The only notable side-effect was supranuclear palsy. This complication can be avoided by exact stereotactic technique. Vegetative symptoms were improved by this operation in several cases. The neurophysiological implications of the results concerning the role of the globus pallidus in genesis of rigidity and tremor are discussed.

Clinical Evaluation of Ambenonium (Mysuran) Chloride. M. R. Westerberg. A. M. A. Arch. Neurol. & Psychiat. **75:**91-94 (Jan.) 1956 [Chicago].

Ambenonium (Mysuran) chloride is N,N′-bis (2-diethylaminoethyl) oxamide bis-2-chlorobenzyl chloride. Pharmacological investigation has shown that ambenonium chloride has anticholinesterase properties that are specific against acetylcholinesterase, with only weak activity against serum cholinesterase, and that its activity is from 5 to 13 times that of neostigmine. In animal experiments, ambenonium was two to four times as active in antagonizing paralysis caused by tubocurarine, and the effect was of much longer duration. The present study concerns the evaluation of the effect of ambenonium chloride in patients with myasthenia gravis. Ambenonium was available in 10 mg. tablets and in scored 25 mg. tablets, so that patients were able to take a 10, 12.5, or 25 mg. dose. Thirty-three patients took ambenonium orally for varying periods of time from August, 1954, to August, 1955. All were ambulatory outpatients who had previously used neostigmine, pyridostigmine (Mestinon) bromide, or tetraethylpyrophosphate (TEPP). Approximately one-third had mild myasthenia, one-third had moderate involvement, and one-third had moderately severe disease. One patient died during the course of the study. Of the 33 patients, 26 found ambenonium to be effective in increasing muscle strength and 7 found it ineffective. Thirteen patients preferred ambenonium to any other anticholinesterase and continued to take it alone. Nine patients considered ambenonium equal to their other medication in its effect, and six of these continue to use it regularly. The toxic effects of ambenonium, which are less than those of neostigmine and greater than those of pyridostigmine, consist of both parasympathetic overactivity and central nervous system stimulation. The drug should be used with caution, and low dosage requirements should be stressed when patients accustomed to taking other anticholinesterase agents change to ambenonium.

GYNECOLOGY & OBSTETRICS

Hemodynamic Effects and Clinical Application of a Mixture of Veratrum and Rauwolfia Alkaloids. J. Voskian, N. S. Assali and L. Noll. Surg. Gynec. & Obst. **102:**37-44 (Jan.) 1956 [Chicago].

Previous studies have shown that the Rauwolfia alkaloid (reserpine) possesses a definite hypotensive action that becomes evident 45 to 60 minutes after intravenous injections of doses of 5 mg. or more. The fall in blood pressure is usually accompanied by somnolence, nasal and conjunctival congestion, and, in some instances, a certain degree of mental depression or anxiety. On the other hand, the intravenous injection of veratrum alkaloids produces a rapid fall in blood pressure followed by nausea, vomiting, perspiration, and epigastric burning. In view of the disturbing manifestations peculiar to both veratrum and Rauwolfia alkaloids the authors thought that a combination of the two agents together in small doses might minimize the incidence of their side-effects yet might have an additive or synergistic action on the blood pressure. Studies were made on 38 pregnant women, including 4 normotensive subjects, 27 patients with preeclampsia, 4 patients with convulsive toxemia, and 3 patients with essential hypertension. The duration of pregnancy varied from 26 to 38 weeks. All patients were at bed-rest in the hospital prior to and during the administration of the drugs. The effective dose of the mixture was found to be 0.1 mg. of protoveratrine or 0.5 mg. of cryptenamine and 2.5 mg. of reserpine. Parenteral administration of this mixture was followed by significant fall in blood pressure, pulse rate, and peripheral resistance. Cardiac output showed insignificant changes. Renal plasma flow and glomerular filtration rate fell at the onset of the hypotensive phase but recovered shortly thereafter despite continued hypotension; renal vascular resistance was consistently reduced. The incidence of side-effects that are peculiar to veratrum and to Rauwolfia preparations was significantly lower after administration of a mixture of the two drugs. It is concluded that a mixture of veratrum and Rauwolfia alkaloids has a number of advantages that make it an excellent adjunct in the therapy of hypertensive diseases.

The Influence of Pituitary Factors on Menopausal Vasomotor Instability. A. A. Hellbaum, J. B. Eskridge III and R. W. Payne. J. Gerontol. **11:**58-60 (Jan.) 1956 [St. Louis].

Menopausal vasomotor instability occurring with waning ovarian function is ordinarily adequately controlled with estrogens. That the beneficial response to estrogen is not merely a replacement phenomenon is evidenced by the observations that vasomotor symptoms in women are also relieved by androgens. A phenomenon common to the administration of either estrogen or androgen is the release of the luteinizing hormone from the pituitary. Twenty-four surgically castrated women with severe vasomotor instability were treated with various pituitary preparations. All of the four patients who received injections of a fractionated pituitary preparation containing predominantly the luteinizing hormone were benefited, while a fractionated pituitary extract containing primarily the follicle-stimulating hormone was without noticeable effect in six patients. An unfractionated pituitary preparation containing both luteinizing hormone and follicle-stimulating hormone alleviated the vasomotor symptoms in 13 of 14 patients. Relief of menopausal vasomotor instability occurs after the administration of luteinizing hormone from the pituitary gland. It is suggested that the beneficial effect of estrogens and androgens on this phenomenon might be due to their release of the luteinizing pituitary factor.

Pregnancy and Extragenital Carcinoma. G. Hebold. Ztschr. Krebsforsch. **60:**621-623 (No. 6) 1955 (In German) [Berlin, Germany].

In the first of the five pregnant women whose histories are presented, autopsy revealed carcinoma of the gallbladder with metastases in liver, sternum, intercostal muscles, vertebrae, and cranium. The woman seemed to be free from carcinoma until the onset of pregnancy. The second woman had cancer of the liver with metastases in the periportal lymph nodes and in the vertebrae. The third had carcinoma of the colon. In the fourth the primary tumor was probably in the lactiferous ducts, but the carcinosis involved the lymph nodes of the anterior mediastinum and of the mesentery, as well as the lungs, the pleurae, and the vertebrae. These four patients had the following factors in common: they were women of an age in whom carcinoma is rare and they had had several births; the primary tumor was relatively small; metastization was rather extensive; and the rapid growth and the formation of metastases coincided with the phase of hormonal transformation, that is, with the first trimester of pregnancy or with the immediate postpartal period. The relative smallness of the primary tumor suggests that changes in the hormonal regulation caused by the pregnancy played a part in the pathogenesis or at least in the rapid growth of the tumor. The fifth pregnant woman had a sarcoma of the mediastinum with metastases in the lymph nodes. Increasing dyspnea had become evident during the second month of pregnancy and she died in the third month. It had been demonstrated experimentally that in the presence of a predisposition to cancer endocrine factors may cause the outbreak of a cancer. Cancers of the male breast have been known to develop in men who received female hormones in the treatment of carcinoma of the prostate.

Reappearance of a Cervical Carcinoma Thirty Years After Treatment with Radium. J. Howkins and J. D. Andrew. J. Obst. & Gynaec. Brit. Emp. **62:**870-871 (Dec.) 1955 [London, England].

In the patient whose history is presented, carcinoma of the cervix was diagnosed in 1925, when the patient was 38 years old. The carcinoma was treated by the vaginal application of 38 mg. of radium. The dose was distributed in 1.5-mg., 2-mg., and 5-mg. needles in and around the portio vaginalis and was left in for 144 hours. One month later a further application of radium needles was made intra-abdominally. The abdomen was opened by a midline incision; a rubber sponge shaped to fit the rectouterine excavation (pouch of Douglas) and carrying 18 radium needles in its lower pole was inserted behind the uterus where it was sutured in position. The radium and its holder were removed 24 hours later. The patient attended a follow-up clinic at yearly intervals until the outbreak of war in 1939. During the whole of this period (14 years), there was no evidence of recurrence of growth. She returned to the follow-up clinic in 1954, over 29 years after her original carcinoma was discovered, with a history of vaginal bleeding. A friable ulcer was found eroding the cervix and infiltrating the vault. Biopsy confirmed the presence of a squamous cell carcinoma. The patient was subjected to laparotomy with a view to performing radical hysterectomy (Wertheim's operation). After the abdomen was opened nearly an hour was spent dissecting the large and small intestine from a dense mass of adhesions in the pelvis. Wertheim's hysterectomy was performed, and the histological study revealed squamous cell carcinoma at the junction of the vaginal vault and cervix, with vaginal spread only. The patient survived. The occurrence of cancer of the cervix nearly 30 years after adequate application of radium can be accounted for in three ways: first, that it is a true recurrence of the primary growth; secondly, that it is a new primary carcinoma appearing at or near the site of the original, and, thirdly, that it is a delayed result of the original radiation treatment. As the original slide is not available, no histological evidence can be adduced to support or refute any of these theories.

PEDIATRICS

Congenital Capillary Hemangiomas of the Parotid Gland: A Lesion Characteristic of Infancy. J. S. Campbell. New England J. Med. **254:**56-60 (Jan. 12) 1956 [Boston].

Three cases of congenital capillary hemangioma of the parotid gland are described in baby girls aged 4 months, 2 months, and 1 month respectively. The three infants underwent subtotal parotidectomies at the ages of 11, 3, and 18 months respectively. There was no recurrence, nine, three, and three months, respectively, after the operation. Of 61 cases of parotid tumors collected from the literature, 60 were in children, and 54 (90%)

of these were hemangiomas occurring in infants in their first year of life. This age distribution is of obvious importance in the differential diagnosis of parotid enlargement occurring before the age of one year. Thirty-six of the 51 patients whose sex was recorded were girls. Evidence suggesting that there is a large number of recognized but unreported cases of the disease is presented. Although these lesions may be one of the variable manifestations of congenital vascular dysplasias involving structures of the head and neck, they have not yet been reported in association with serious intracranial vascular anomalies. The chief danger inherent in parotid hemangiomas appears to be permanent damage to the facial nerve during surgical removal. In two of the author's patients this complication did not occur; in one patient a complete facial palsy was noted on the first postoperative day, but three months after the operation the only evidence of residual facial nerve damage was slight asymmetry of the mouth in smiling. The planned resection of portions of the facial nerve as part of primary excision for this lesion could be described as an unwarranted procedure.

Streptomycin–Isoniazid–Hydrocortisone Combination Given Intrathecally in Early Treatment of Tuberculous Meningitis. R. Cocchi. Riv. clin. pediat. **56:**229-243 (Sept.) 1955 (In Italian) [Florence, Italy].

The administration of streptomycin, isoniazid, and hydrocortisone by cisternal injection brought about the recovery of 15 patients (three of them children) with tuberculous meningitis to whom the preparations were given soon after the onset of the condition. The therapeutic regimen was as follows: the patients received daily, according to age and weight, from 300 to 500 mg. of streptomycin intramuscularly and intravenously by drip instillation and from 500 to 900 mg. of isoniazid orally and intravenously by the same method. The adult patients, and especially those whose condition was most severe, received, besides this therapy, 2 mg. of streptomycin, 20 mg. of isoniazid, and from 2.5 to 5 mg. of hydrocortisone every 12 hours by cisternal injection. Children and adults whose condition was less severe were given a cisternal injection of 20 mg. of isoniazid and from 2.5 to 5 mg. of hydrocortisone, and this was alternated every 12 hours with a lumbar injection of 30 mg. of streptomycin and 40 mg. of isoniazid. Three patients were given hydrocortisone by the lumbar and the cisternal routes concurrently, but the results were no better in these patients than they were in those who were given the hormone by the cisternal injection alone. The intravenous drip administration of streptomycin and isoniazid was suspended after one month, whereas therapy by the cisternal route was suspended only after the spinal fluid protein level had become normal. Administration of the antibiotics was continued thereafter by spinal injections given every 24 hours until a complete recovery was secured. The improvement was surprising and was brought about much more quickly than when other therapeutic regimens are used. The average time required for recovery was 71 days. This antibiotic-hormone combination is extremely valuable in the treatment of tuberculous meningitis. It restores to normal the spinal fluid circulation, prevents the formation of blocks, and brings about a rapid and frank fall in the altered protein level of the fluid.

Considerations on Action of Procaine Given Intravenously to Nurslings with Severe Toxicosis Caused by Gastroenteritis. M. Giusti. Riv. clin. pediat. **56:**244-266 (Sept.) 1955 (In Italian) [Florence, Italy].

The slow intravenous administration of from 2 to 4 cc. of a 1% procaine solution diluted in isotonic sodium chloride solution or in a glucose solution proved to be an efficacious adjuvant in the treatment of nurslings with acute toxicosis, especially when this was secondary to severe gastroenteritis. Giusti has been using this method since 1947 and has obtained good results without side-effects or signs of intolerance. The effect of the procaine is immediate though temporary, with a sudden improvement in the general condition, more regular and more efficient respiratory and cardiovascular action, a return to normal of the blood level of chlorides, protein, and potassium, and better water and salt metabolism. This improvement makes it possible to institute the main therapy immediately after the procaine injection. These immediate changes as well as others that are sometimes observed (nystagmus, clonic jerkings of upper extremities and head, and eventual crises of apnea) suggest that the drug exerts its action on the autonomic nervous system and the nerve centers, which are greatly impaired by the severe toxicosis. The drug also exerts a peripheral action by inhibiting the chemical mediators or by stimulating the peripheral syncytial centers or by bringing about a certain functional balance in the peripheral organs so that the exchange between the blood and the tissues can be reestablished. As a consequence of the action of the procaine, the organism is capable in most instances of overcoming the severe crisis caused by the toxicosis and of benefiting from the main therapy. The prognosis of acute toxicosis in nurslings can be based on the results of the procaine injection. Experience at the author's clinic has proved that, when the injection is not followed by the immediate changes mentioned above, the condition of the infant deteriorates and death often ensues.

The Etiology of Pre-Adolescent Kyphosis. A. B. Ferguson Jr. J. Bone & Joint Surg. **38A:**149-157 (Jan.) 1956 [Boston].

A study of the roentgenograms of the chest of 153 unselected children between the ages of 6 and 11 years with normal development of the spine revealed that the normal kyphos is principally in the proximal portion of the spine at the fifth, sixth, and seventh thoracic vertebrae. This study also showed that the time for normal closure of those vertebral bodies developing with a persistent anterior vascular groove is in the age group between 7 and 10 years. Twenty-one patients between the ages of 5 and 17 years with dorsal-wedging round back deformity and varying involvement of thoracic vertebrae from the 6th to the 12th were examined roentgenographically and were followed up for one to nine years. Progression of round back deformity was observed in 18, all of whom had persistent anterior vascular grooves. It appears that persistence of the anterior vascular groove in the bodies of the thoracic vertebrae may play a role in the production of deformity by inviting anterior collapse of the vertebrae. Actual round back deformity is the result of wedging of the vertebrae below the region of the fifth, sixth, and seventh thoracic vertebrae. This wedging accentuates the normal kyphos. There is sufficient evidence to warrant treatment of children in the age group between 8 and 14 years who show this sign on chest roentgenograms and who present early clinical evidence of poor posture with round back and increased lumbar lordosis.

DERMATOLOGY

Lupus Erythematosus: Clinical and Hematological Studies in 77 Cases. R. H. Marten and E. K. Blackburn. A. M. A. Arch. Dermat. **73:**1-14 (Jan.) 1956 [Chicago].

Many hematological abnormalities have been described in disseminated lupus erythematosus, including hypochromic and hemolytic anemias, leukopenia, granulopenia, eosinophilia, thrombocytopenia, increased erythrocyte sedimentation rate, cold agglutinins, a positive direct Coombs' test, and lupus erythematosus (L. E.) cells. The hematological state of patients with the chronic discoid form of lupus erythematosus has, however, received relatively little attention. The authors performed clinical and hematological studies on all patients with lupus erythematosus attending the Department of Dermatology at The Royal Infirmary in Sheffield. Additional patients with lupus erythematosus were referred to the authors from other hospitals. Patients in whom the clinical and/or histological diagnosis was in doubt were excluded. The series of 77 patients included 66 with the chronic discoid disease, 6 with the generalized discoid type, and 4 with subacute and one with acute disseminated lupus erythematosus. The following studies were made on all patients: hemoglobin level estimations, red blood cell counts, total and differential leukocyte counts, platelet counts, erythrocyte sedimentation test, direct Coombs' test, and determinations of the cold agglutinin titer and of the presence of L. E. cells. Hematological abnormalities were found in over half of the 66 patients with chronic discoid, in 5 of the 6 with generalized discoid, in

all 4 with subacute disseminated, and in the single patient with acute disseminated lupus erythematosus. Within the group of those with the chronic discoid form, a clinical comparison between those showing normal and those showing abnormal hematological findings failed to reveal any definite means of foretelling on clinical grounds which patients would show such abnormalities. The significance of the hematological abnormalities in patients with the chronic discoid form of the disease can only be assessed after a prolonged clinical and hematological follow-up.

Lupus Erythematosus Profundus: Commentary and Report of Four More Cases. H. L. Arnold Jr. A. M. A. Arch. Dermat. 73:15-33 (Jan.) 1956 [Chicago].

The infiltrated forms of lupus erythematosus have been divided into three categories: (1) lupus erythematosus tumidus, characterized by relatively transitory elevated, edematous, erythematous plaques, the "acute discoid" variety of Michelson; (2) lupus erythematosus hypertrophicus, characterized by raised, plateau-like plaques with rolled edges and central atrophy and scaling, called lupus erythematosus hypertrophicus et profundus by Bechet; and (3) lupus erythematosus profundus, characterized by sharply defined firm nodules lying beneath unaltered or moderately erythematous skin. The author feels that the choice of the adjective profundus for the last-named category was a somewhat unhappy one on two grounds: it does not clearly indicate that the lesions are clinically subcutaneous rather than merely "extending deeply," and it invites confusion with a different lesion, Brocq's "lupus erythemateux profond," which was either lupus vulgaris or else the same as Bechet's lupus hypertrophicus et profundus. The term lupus erythematosus subcutaneus might have been preferable, but the name lupus erythematosus profundus has been applied to such nodular lesions by Irgang, Arnold, Costa and Junqueira, and Ramos e Silva and Portugal. On the basis of 11 previously described cases and 4 cases presented in this paper, the author concludes that sharply defined, firm, painless nodules occurring under clinically unaltered skin may rarely appear as a manifestation of lupus erythematosus. Epidermal changes characteristic or suggestive of lupus erythematosus; fibrinoid necrosis of collagen; and prior, concurrent, or subsequent development of ordinary discoid lupus erythematosus provide evidence that these nodular lesions are, in fact, a part of this disease process. The relationship of these persistent nodules to the transitory edematous nodules occurring in the vicinity of joints in some cases of systemic lupus erythematosus (and in some cases of rheumatoid arthritis) is not clear. It seems probable, however, that they are not the same. Systemic involvement has been lacking in most cases of lupus erythematosus profundus, and the nodules have been persistent and, for the most part, remote from joints. Lupus erythematosus profundus is an unusual clinical variety of lupus erythematosus in which the cutaneous infiltrate occurs primarily (though not always exclusively) in the deeper portion of the corium, with only microscopic epidermal changes, giving rise to firm, sharply defined nodules from one to several centimeters in diameter lying beneath clinically normal or nearly normal skin.

Antimalarials in the Treatment of Discoid Lupus Erythematosus: Special Reference to Amodiaquin (Camoquin). R. W. Leeper and M. F. Allende. A. M. A. Arch. Dermat. 73:50-57 (Jan.) 1956 [Chicago].

Antimalarial drugs such as quinacrine (Atabrine) hydrochloride and chloroquine (Aralen) phosphate have been used effectively in the treatment of discoid lupus erythematosus, and more of these drugs are being investigated in an effort to find those that are most beneficial and at the same time least toxic. The studies described here are concerned with quinacrine, chloroquine, and amodiaquin (Camoquin) hydrochloride, and they were made on 32 patients. The results obtained with quinacrine were consistent with reports by other observers. Chloroquine was used in 29 patients, of whom 15 had previously responded to quinacrine. After having received both drugs, they expressed a preference for the latter on grounds of better tolerance, absence of skin discoloration, and, except for one patient, more convincing improvement. All except two of the patients who had received no other antimalarial prior to chloroquine fared well on it. Relapses after chloroquine therapy seem to respond well to retreatment with chloroquine. Amodiaquin is a yellow, crystalline powder resembling quinacrine in appearance but not producing discoloration or fluorescence in the skin. It is available in tablets of 0.2 gm. Chemically, amodiaquin is, like chloroquine, a derivative of 7-chloro-4-aminoquinoline. No injury was reported from its use. Of the 16 patients who were treated with amodiaquin, 8 had received both quinacrine and chloroquine previously, 6 had received chloroquine previously, and 2 had received no other antimalarial drug. Most patients received one tablet of amodiaquin daily. The tolerance for amodiaquin was excellent. Its therapeutic effect is similar to that of chloroquine. More clinical investigation of amodiaquin is necessary to determine its safety. The antimalarials do not cure the disease, but they induce a remission. Relapses usually respond to retreatment.

Mepacrine and Chloroquine in the Treatment of Rosacea. H. Brodthagen. Brit. J. Dermat. 67:421-425 (Dec.) 1955 [London, England].

Mepacrine hydrochloride and chloroquine phosphate have proved effective in the treatment of lupus erythematosus, which is often provoked by sunlight. The author describes therapeutic experiments with these drugs in 57 patients with rosacea. The group included patients with quite mild as well as very severe cases, but the great majority showed moderate redness as well as a moderate number of pustules and infiltrations. The main complaints were itching and burning, especially brought on by fluctuations in temperature and by stormy weather. Twenty-three were certain that exposure to sunlight was a provocative factor. As criteria of the effect of treatment, the author counted subsidence of infiltrations, pustules, and diffuse redness as well as diminished subjective sensations in the lesion. As telangiectasia remains unaffected, it was not included among the criteria. Twenty-one patients received mepacrine and 36 were treated with chloroquine. A total of 70 courses was completed, 13 patients having 2 courses. The dosage was two tablets daily during the first 10 days and then one tablet daily for a minimum of three weeks (the mepacrine tablets contain 100 mg. and the chloroquine tablets 200 mg.). In the cases treated with mepacrine the maximum treatment period was 10 weeks and the maximum dose 10 gm.; the corresponding values for the chloroquine cases were 15 weeks and 28.4 gm. The patients were tested for light tolerance with a mercury lamp while not under treatment. Eighteen patients were rendered symptom-free by mepacrine or chloroquine. Sixteen of the cured patients belonged to the group of 23 who had observed that the lesions were provoked by sunlight. The effect was most marked in the months with highest intensity of ultraviolet light and most hours of sunlight. The effect observed in a few other cases presumably represents only spontaneous fluctuations. It is likely that the effect of mepacrine and chloroquine upon rosacea is due to the capacity of these drugs to increase the light tolerance. Therefore, this treatment should be reserved for cases in which the light provocation has been definitely ascertained by the patient himself, as the susceptibility of the skin to quantitative irradiation does not appear to afford any guidance.

Overtreatment Dermatitis. L. E. Gaul. Ann. Allergy 13:642-653 (Nov.-Dec.) 1955 [St. Paul].

The author presents the histories of 14 patients with overtreatment dermatitis observed during the first three months of 1955. During this period, overtreatment dermatitis was the most prevalent skin disease observed. Past-treatment patch tests made on 90 patients resulted in plus reactions in 56. Remedies producing one to two plus reactions were, for the most part, those the ingredients of which included the essential oils and salicylic and benzoic acid. Three to four plus reactions were produced by the organomercurials, antibiotics, "caine compounds," and antihistamines. Asking patients with dermatological disorders to bring in the remedies they have used and having them make a special effort to find those that have been mislaid or borrowed will reveal many that elicit positive patch tests. When making past-treatment patch tests, it is advisable to use the medicines

the patient brings in. A severe reaction—massing of vesicles, bullae, and flaring—to their own medicine is looked upon differently than when the preparation is taken from a testing tray. Case histories show that mixing remedies always favors the development of overtreatment dermatitis. One patient had used eight different remedies to treat a finger injured with a screw driver. A baby in whom a number of solutions, salves, soaps, lotions, and powders had transformed a small area of rash to a generalized dermatitis was finally restored to health after all treatment was stopped. Patients will often resort to self-treatment while under the care of a physician, and the therapeutic agents used by the patient as well as those used by the physician may prove to be sensitizing substances.

Anaphylactoid Purpura (Henoch-Schönlein's Syndrome): Clinical Study of Forty-Five Cases. L. Sánchez Medal and E. Reynoso. Rev. invest. clín. **7**:293-312 (July-Sept.) 1955 (In Spanish) [Mexico, D. F., Mexico].

Forty-five patients with anaphylactoid purpura (Henoch-Schönlein's syndrome) were observed at the Hospital de Enfermedades de la Nutrición, Mexico City. The patients were adults except for one 3-year-old child. Most of the patients were between the ages of 20 and 30 years. Purpura appeared in all cases either as the first symptom or in the course of the first three weeks of the disease. In more than half the patients the purpuric lesions were papulous and confluent, with extensive zones of local congestion, hemorrhage, and ecchymosis. The skin and mucosa of the face appeared to be immune to the development of lesions of anaphylactoid purpura. Sixteen patients had arthralgia of multiple localization and 24 had abdominal disorders. Abdominal colicky pain was often associated with nausea, vomiting, and gastrointestinal hemorrhage. Pain was so acute in some that constant administration of analgesics or antispasmodics was necessary. The 3-year-old child developed an ileoilial gangrenous intussusception that called for resection of the gangrenous loop. The patient recovered. A patient with acute pain in the epigastric region and in the right iliac fossa, in whom exanthem had not as yet appeared, had an erroneous diagnosis of acute appendicitis, and an appendectomy was performed. Glomerulonephritis of the type of hemorrhagic nephritis appeared in about the sixth week of the disease in eight of the younger patients. There was albuminuria in all patients with renal complications, erythrocyturia in seven, cylindruria in three, uremia in three, and arterial hypertension in one. One of the patients with purpuric nephropathy died as the result of cardiac failure. Histopathological study of the kidneys removed at autopsy showed changes characteristic of subacute glomerulonephritis. Anaphylactoid purpura in itself is not a fatal disease. The disease may subside spontaneously and the patient be cured, or the cutaneous lesions may become chronic. The appearance and course of the renal complication determines the prognosis. A fatal termination is, as a rule, due to nephritis. Intestinal complications, intussusception, and perforated necrosis with consequent peritonitis are less frequent. Transient neurological disorders, severe visceral hemorrhages, and necrosis of the myocardium are extremely rare complications of anaphylactoid purpura. In the cases observed by the authors, all the usual treatments were attempted without success. It was found that only absolute bed rest and administration of cortisone or ACTH had a favorable effect on the symptoms. The effects were excellent in abdominal symptoms, fair in articular symptoms, mediocre for the cutaneous lesions, and nil for the renal disease.

ANESTHESIA

The Status of Refrigeration for Amputations and for Tissue Preservation. L. W. Crossman. Am. J. Surg. **91**:92-98 (Jan.) 1956 [New York].

Refrigeration anesthesia for amputations received wide and enthusiastic adoption in 1942, but it later fell into disuse except in poor-risk cases. The author feels that the fact that the use of refrigeration remains unquestioned as anesthesia for these desperate cases is evidence that the disuse has not been due to any failure of the method. The real reason has been that other methods have been found more convenient. The author applies refrigeration anesthesia in the following manner: The head of the bed is elevated on 10 in. blocks, and the mattress is protected by a rubber sheet. Three long strips of bandage are laid transversely across the bed at the levels of the thigh, ankle, and halfway between, respectively. A woolen blanket is laid on them, and three more strips of bandage are placed across it. A rubber half-sheet is then superimposed from groin level to below the feet. A tourniquet is applied around the thigh, and the leg is buried from the toes to near the groin in approximately 75 pounds of finely chopped ice. The rubber half-sheet is wrapped around the leg and tied snugly with the three lengths of bandage already in position. The lower end of the rubber half-sheet is draped as a gutter to carry water from the melting ice into a bucket at the foot of the bed. Finally, the woolen blanket is wrapped around everything and fastened with the bandage strips that were laid outside it. The blanket acts as an insulator so that melting is minimized and the ice generally requires no renewal. The tourniquet can be omitted under some circumstances. The leg is not removed from the ice until after the surgeons are scrubbed; then it is dried, the skin is prepared, and the amputation is performed as usual. The major reasons for using refrigeration are to avoid shock, to control intoxication, and to avoid anesthetic accidents. To show that preservation of tissues may be facilitated by refrigeration anesthesia, the author cites a patient who had severed a finger, which was hanging only by a shred of skin. By telephone, the patient was instructed to place the finger in ice water. When the physician reached the patient several hours later, the part was sutured in place and kept in an improvised ice pack for four days, with gradual raising of the temperature during this time; healing followed. Burns involve essentially the same therapeutic principles as mechanical trauma. Refrigeration is the only agent that can simultaneously inhibit pain, shock, infection, and tissue devitalization. It is the ideal treatment. The best emergency treatment is to plunge the burned part immediately into ice water or the coldest water obtainable. The physician should dress the area with a single layer of petrolatum gauze and apply ice or a refrigerating applicator at ice temperature. The duration of hypothermia depends on the severity of the burn, ranging from a few hours for a minor burn to several weeks when needed. Cleansing of burns or mechanical trauma by means other than the gentlest rinsing will remove or injure tissue, which regenerates surprisingly well under refrigeration, often obviating the need for skin grafts. The absence of pain, opiates, and intoxication promotes systemic strength and appetite. The customary extreme aseptic care is unnecessary under this treatment.

Steroid Anesthesia in Man: Clinical and Cerebral Metabolic Effects. G. S. Gordan, N. Guadagni, J. Picchi and J. E. Adams. J. Internat. Coll. Surgeons **25**:9-12 (Jan.) 1956 [Chicago].

The water-soluble sodium salt of the steroid 21-hydroxypregnanedione sodium succinate (Viadril) was administered intravenously without barbiturate or narcotic premedication to five schizophrenic patients and to three normal persons. Anesthesia, consisting of loss of consciousness, insensibility to pain, absence of corneal reflex, and presence of muscular relaxation, was produced in six of these persons. Two persons were given the drug only to the point of hypnosis; these two had pronounced salivation, which was prevented in subsequent patients by first administering 0.6 mg. of atropine sulfate intravenously. Respiratory depression did not occur during the slow intravenous infusion of Viadril in these eight persons. Hypnotic and anesthetic effects were induced after a lag period of 3 to 10 minutes after the slow intravenous administration of the drug. Recovery was rapid, and patients were able to reply to questions 18 to 40 minutes later. Seventy-three minutes were required for recovery in a patient who was given 2 gm. No untoward after-effects were observed except for pain in the antecubital fossa and forearm of one patient. Hemolysis did not occur after the administration of Viadril. When this drug is administered intravenously, it produces anesthesia and cerebral metabolic changes identical with those produced by barbiturates but without respiratory depression.

BOOK REVIEWS

Cancer and Common Sense. By George Crile Jr., M.D. Cloth. $2.75. Pp. 118. The Viking Press, Inc., 18 E. 48th St., New York 17, 1955.

Dr. Crile discusses cancer and the end-results obtained by our present methods of treatment with frankness and sincerity and without fear. He devotes one chapter to the zone of diminishing returns, indicating that medical men have probably reached the zenith as far as the present modes of attack are concerned. It is edifying to read that "in faith and philosophy there are comforts that science cannot give." The idea of the author that fear planted in the minds of the laity has given rise to cancerphobia is not new but merits presentation to the medical profession. The writer discusses the nature of both early and late cancer and the end-results obtained, and he attributes success and failure in many cases to the type of malignancy and the age of the patient rather than to the type of curative attack. He believes that surgery is not always the answer to serious cancer problems but is, in light of our present knowledge, often the best treatment when combined in certain instances with the various types of radiation, endocrine therapy, the isotopes, and in some cases adrenalectomy.

The writer believes that some surgeons have become technical perfectionists and have lost sight of reality and perform operations that are more dangerous than the disease. Ultrasurgical procedures and needless operations are frankly discussed by the author, who does not criticize the contributions made by radical surgeons but calls to account those who persist in harmful practices and do not learn by their mistakes. In our day of intensive surgical training, when many young men with perfect surgical technique but lacking experience and judgment enter the field of surgery feeling that the aseptic scalpel is the only answer, Dr. Crile's work may cause surgeons young and old to consider what course they would pursue in their own families, and this is apparently the purpose of his book. It is not a textbook or a reference book, but it covers many controversial issues in the field of cancer treatment. It should be read by all physicians. Honest disagreement in medical ranks leads to progress. The book might be considered a bombshell in nonmedical hands. Dr. Crile's philosophy is that "it is the privilege of those who die to realize that their death is part of their life." In any event, Dr. Crile looks facts in the face, and this course may be the avenue to greater progress if these opinions are seriously considered by both physician and patient. He looks forward to newer therapies and the prevention and cure of cancer.

Ciba Foundation Symposium on Experimental Tuberculosis: Bacillus and Host. With an Addendum on Leprosy. Editors for Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., and Margaret P. Cameron, M.A., A.B.L.S., assisted by Cecilia M. O'Connor, B.Sc. Cloth. $9. Pp. 396, with 69 illustrations. Little, Brown & Co., 34 Beacon St., Boston 6, 1955.

The Ciba Foundation, London, is an educational and scientific charity founded by a trust deed in 1947. It provides an international center where workers active in medical and chemical research are encouraged to meet informally to exchange ideas. In the first five years there have been 29 symposiums, and others are planned at the rate of five or six a year. The proceedings are issued in full with a minimum of editing. They present in book form much readable information not readily available elsewhere. Leading research workers from different countries and in different disciplines are invited to attend the symposiums, but the size of the group is limited. Among other aspects of the general subject, this volume deals with the protein of the tubercle bacillus, chemical structure and biological activity of mycolic acids, polysaccharide components, tissue reactions to bacilli and their products, biochemical factors, serology of polysaccharides, bacilli as immunologic adjuvants, hypersensitivity and desensitization, bacterial multiplication in immunity, human lung tissue reactions and chemotherapy, a pathogenic relationship between tuberculosis and leprosy, reaction of host tissue to Mycobacterium leprae, and the immunologic and physiological basis of immunization in tuberculosis and leprosy. Most of the papers are informative and of high caliber in that they present direct scientific information on the nature of the tubercle bacillus and reactions of the host, but one wonders on reading the discussions (wasteful of space and time) whether they could not have been deleted or at least condensed. The spirit of the symposium is laudable, but a brief presentation of the valuable pertinent information might serve a wider audience. The book leaves one, to quote Rich, "richer in ideas and in an understanding of the present limits of our knowledge." Progress against tuberculosis is slow and far from complete as yet, but this book should serve as a stimulus to all students and investigators.

American Foundations and Their Fields. By Wilmer Shields Rich. Seventh edition. Cloth. Pp. 744. American Foundations Information Service, sponsored by Raymond Rich Associates and Marts and Lundy, Inc., 860 Broadway, New York 3, 1955.

The role of the American foundations and the fields in which they operate in the United States are not well understood. This book, which is in its seventh edition, describes more than 4,000 foundations. There are more foundations than are listed in the book, but many operate in such a way that information concerning them is not readily available. For example, it has been estimated by the author that, if information could have been practically obtained on all foundations, descriptions of 7,300 might have been included. Sources of reliable information have suggested the existence of as many as 30,000 foundations, but many of these are small and restricted to extremely limited fields. Following an introduction describing foundations in general, the states and the foundations operating in them are alphabetically listed. The information is in brief but pointed form; for example, for most foundations the name, address, where incorporated, donors, principal methods of operation, financial data, and officers are given. Supplementing this information is a practical and worthwhile index of foundation names. In turn this is supplemented by another index of the fields of operation for the foundations described so that one may either look up a foundation by name or turn to a subject, for example, cancer, and find reference to the foundations interested in this disease. The book is not confined to medical research foundations. Like the earlier volumes, this edition should be useful to those who seek information on American foundations.

Feeding Your Baby and Child. By Benjamin Spock, M.D., and Miriam E Lowenberg. Ph.D. Cloth. $3.75. Pp. 226, Duell, Sloan and Pearce—Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

This current volume, written in collaboration with Dr. Lowenberg, is a welcome companion to Dr. Spock's popular "Common Sense Book of Baby and Child Care." Dr. Spock's common sense and Dr. Lowenberg's wide experience in the feeding of children make this child care cookbook a valuable volume for any home with children. Not only is basic nutritional information presented in a relaxed informal manner, but other practical topics such as diet during pregnancy and lactation, infancy, and illness as well as feeding problems are discussed. In addition, there are many recipes that not only are good for children but also are likely to be popular with the entire family. Four weeks of sample menus for the main meal of the day are included for each season of the year. These menus are planned for use by the entire family. Throughout the book are scattered practical hints on how both the parent and the child can obtain more enjoyment from meals. The mother should find the recipe index especially helpful. This is a book that should be particularly useful to the expectant and new mother, supplementing the feeding instructions of the physician.

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

QUERIES AND MINOR NOTES

ENZYMES USED IN MEAT TENDERIZING

To the Editor:—*Is there any reliable information on whether the enzymes used in meat tenderizing, which are now so widely advertised, have any deleterious affect on the human body over a long period of time? Also, are there reasons to believe that the administration of hormones to capons or the common use of antibiotics in animals used for meat might result in any damage over a long period of time?*

M.D., Virginia.

Answer.—There is no reason to believe that the enzymes used in meat tenderizing have any deleterious effect. Two enzymes widely used for this purpose are papain, prepared from the edible papaya, and bromelin, which is prepared from pineapple. These enzymes are proteases and merely supplement the enzymatic partial digestion of meat that occurs during autolysis. The products formed are normal products of the digestion of protein. Estrogen administration to poultry is controlled in such a manner that no detectable quantity of the estrogen appears in the meat. The hormone is sometimes implanted as a pellet in the neck in such position that any residual quantity would be removed in processing. Although antibiotics in small quantities are contained in some feeds, present regulations in this country do not allow detectable quantities of administered hormones or antibiotics to appear in the meat. In only one instance is the use of antibiotics during processing sanctioned at present. This is in the processing of ready-to-cook poultry. Under conditions of use none of the antibiotic remains in the cooked poultry.

PSORIASIS

To the Editor:—*I would like information on the grafting of skin on a patient who is entirely covered with psoriasis. Any donor area that can possibly be used is completely involved with psoriatic lesions. It appears that any skin graft, because of the excessive thickening of the skin due to psoriasis involvement, would be too thick to make it feasible for use in grafting.* *Howard D. Cogswell, M.D., Tucson, Ariz.*

This inquiry was referred to two consultants, whose respective replies follow.—Ed.

Answer.—If blood supply were the only factor involved one could expect a successful outcome from skin grafting of psoriatic skin, for such skin has an excellent supply of blood. In the course of experimental studies wherein small areas of normal skin and psoriatic patches have been transposed, the grafts were successful but psoriasis appeared in both areas.

Answer.—Presuming the necessity for skin grafting and accepting the statement that all possible donor areas are involved with psoriasis, the doctor has no alternative but to use involved skin unless the temporary benefit from homografts will be sufficient. Actually, the problem is not as serious as it sounds because psoriasis is a disease of the epidermis with excessive scaling, and the corium is not involved except for vascular dilatation that would cause increased bleeding from the donor site. Preferably, the doctor should remove the thick, scaling layer before taking the skin graft, either by scrubbing with a brush or, if time permits, by ultraviolet therapy for about 10 days. Whether or not the scale is removed, the dermatome setting has to be determined by trial and error in order to get deep enough to obtain a viable graft. The scaly surface should not necessarily hinder a take, and both donor and recipient sites should be managed in the usual manner.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

SUSCEPTIBILITY TO POLIOMYELITIS

To the Editor.—*A father of three children wonders about the advisability of giving all his children poliomyelitis vaccine, since he feels there must be some inherited weakness that predisposes the family to poliomyelitis. In 1918 the maternal grandfather, in 1932 the mother, and in 1946 the oldest daughter, had poliomyelitis.*

K. G. Vandergon, M.D., Portland, N. D.

Answer.—The possibility of familial or hereditary susceptibility to poliomyelitis has long been discussed but has not been satisfactorily established. When cases occur in families as indicated, one is tempted to wonder whether chronic carriers of poliomyelitis exist even though they have not been demonstrated. Whatever the basis, there is no contraindication to the giving of vaccine to all the children in a family.

REACTION FOLLOWING USE OF TRIPLE VACCINE

To the Editor:—*A one-year-old boy in good physical condition was given his first injection of 0.5 cc. of triple vaccine. Six hours later he became irritable and had a rectal temperature of 101 F (38.4 C). During the next 12 hours irritability continued to increase and maximal temperature was 103 F (39.5 C). He was then started on therapy with aspirin and Multihist syrup. On the third day he started to improve; temperature and irritability subsided, and therapy with medicaments was discontinued. What precautions should be taken when he receives his second and third injections of the triple vaccines? Is this to be considered an allergic reaction?*

M.D., Illinois.

Answer:—It is not rare for reactions, such as the one described, to occur when instituting active immunization with the triple antigens. Nevertheless, when giving the second immunizing injection, it would be precautionary to omit the pertussis vaccine. If it seems advisable, immunization against whooping cough may be undertaken after completion of the diphtheria and tetanus toxoid injections. Should a severe reaction follow when pertussis vaccine alone is administered, no additional injection of this vaccine should be made. The term "allergic" may be applied to the reaction that was experienced by the child.

NITRITES AND GLAUCOMA

To the Editor:—*The nitrites, as used in angina pectoris, are said to be contraindicated in the presence of glaucoma. Yet some cardiologists and ophthalmologists prescribe them despite the presence of glaucoma. Is glaucoma an absolute contraindication to the use of nitrites? If not, what may be done for a person with mild anginal attacks and glaucoma insofar as coronary vasodilators are concerned?* *M.D., New York.*

Answer.—Cristini and Pagliarani (*Brit. J. Ophth.* 37:741, 1953) found that amyl nitrite inhalation caused a decrease in intraocular tension in most patients with simple glaucoma. In congestive glaucoma the tension frequently rose briefly. These changes did not occur in unison with variation in the brachial blood pressure. Many studies with autonomic drugs indicate that the intraocular pressure rapidly adjusts to changes in systemic blood pressure and volume of the intraocular blood vessels. This homeostatic mechanism is probably defective in glaucoma—hence the caution advised in the administration of such drugs in this disease. However, it is believed that it is extremely unlikely that coronary vasodilators would prejudice the treatment of glaucoma, and certainly there is no absolute contraindication to their use. Far more dangerous to patients with glaucoma are the drugs, such as belladonna, Banthine, and the like, used in the treatment of gastrointestinal disease.